Issue #04 November 2016

Amsterdam Science

Lighting up the brain

Art and science

Building synthetic cells

Science is art!

The fourth issue of Amsterdam Science continues where the last issue ended, as that was with a reference to the website of New Realism. Now a compilation of artistic images produced by scientists and collected in the New Realism project graces the back cover of issue #4. Art also meets science in this issue's interview with Robert van Langh, chairman of the Netherlands Institute for Conservation, Art and Science (NICAS). Dip into the world of art conservation, restoration and forensic research. How can the identity of a renaissance statue be established? What's the right way to restore a Rembrandt? Or even better - how to prevent deterioration of our cultural heritage? Van Langh's passion for art and science shines through, as does his yearning to understand the ageing processes that threaten all works of art. In a related short article, Joen Hermans tells how chemists have uncovered that the ageing processes in oil paintings are all about soap! From science reaching out to art it is a small step to outreach to a broader public: Michiel Buchel, general director and chairman of the board of NEMO in Amsterdam, the largest science centre in the Netherlands answers our questions on the Q&A page of this issue. Read in this issue what his dreams are about King Willem Alexander!

Being a plant biologist myself I am proud to have an iconic plant species feature on the cover in the guise of a petunia flower. The history of this now very common bedding plant and its historical link with the city of Amsterdam is revealed in the Then&Now section. As ever we have a stunning centrefold: this time a close-up look at the mobile human cells that kick-start the formation of blood vessels. Fully in line with the "Science is art!" leitmotif of this issue, a handsome infographic features one of the most innovative techniques in brain research, namely optogenetics. Huub Terra and Esther Visser from the Center for Neurogenomics and Cognitive Research (CNCR) at the Vrije Universiteit, Amsterdam describe how lighting up the brain can help us understand brain function.

Issue four is packed with much more to enjoy from the fields of astronomy, physics, life science, chemistry, computer science and medical research. We're delighted to present a trio of debuts in Amsterdam Science's: from the Amsterdam Medical Centre, from the Institute for Logic, Language and Computation and there is a long article illustrating biophysics research from the AMOLF Institute, in which Gijsje Koenderink describes how she combines a minimal set of cellular components into a cell-like system, so as to study the physical constraints of cellular movement.

Amsterdam Science doesn't just present a selection from the rich variety of science that is made in Amsterdam, it also challenges us to think again on issues we may take for granted. In this vein, Jean-Sébastien Caux's column challenges us on the concept of Open Access, and he closes his contribution with the statement: "the question is not whether science should be open or not. The real question which remains is: how open are you?" Something to reflect on after taking in the eclectic mix of science for art, science as art and artful science that is issue four of Amsterdam Science.

On behalf of the Editors-in-Chief
Michel Haring

ABOUT THE COVER IMAGE:
Part of a *Petunia hybrida* flower visualizing the activity of 'jumping genes' (also known as transposons). In the white areas of the flower, a gene for flower colour formation has been disrupted by the insertion of the transposon. If this transposon 'jumps' out of the gene again, flower colour biosynthesis is restored and cells, or even larger parts of the tissue, regain their characteristic red colour. More information on page 11.

Image credit: Jan van Arkel, IBED, UvA

colophon

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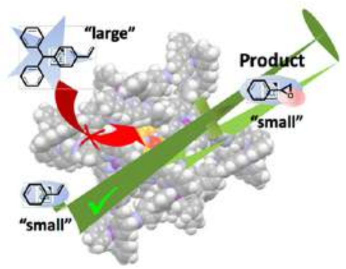
Catalysis inspired by nature

PETRUS KUIJPERS is PhD student in Chemistry in the group of Homogeneous, Supramolecular and Bio-inspired catalysis, UvA.

→ In living organisms, enzymes are capable of catalysing a broad range of chemical reactions under mild conditions. Metallo-enzymes, for instance, easily convert nitrogen from the atmosphere into ammonium. However, the same conversion in industry using the so-called Haber-Bosch process requires a high pressure (200 bar) and temperature (500 °C), which means that just this one reaction is responsible for ~1% of the worldwide energy consumption. We have explored a different approach: mimicking the function of enzymes to reduce the amount of energy used by the chemical industry. Metallo-enzymes generally contain an active (metal-based) centre where catalysis takes place, yet the remaining protein structure still influences the catalysed reaction in three ways. First, it protects the embedded active centre from destructive side-reactions. Secondly, the protein structure can organize the reacting molecule in such a way that much milder conditions are sufficient to perform the transformation, consuming less energy. Finally, the structure helps to maintain high substrate-selectivity by preventing molecules that have the wrong shape or size to reach the active centre. Therefore, inspired by naturally occurring enzymes, we have tried to construct a protective environment around our catalysts, hoping to provide a 'proof of principle' for this approach. Preparing a complete enzyme environment in the lab would be extremely challenging. Instead, we decided to functionally mimic the protein environment using a supramolecular cage, as depicted in grey in the Figure. The cage is made by mixing three building blocks: an iron salt, a porphyrin and a functionalised aldehyde. Much like natural enzymes, these components spontaneously self-assemble to form the supramolecular cage. We have shown that this cage structure is able to maintain the activity of the catalytic centre twice as long as its unprotected counterpart. Furthermore, the size of the 'windows' in the cage has been shown to put a limit on the size of molecules that are able to reach the active centre. This trick allowed us to selectively convert small molecules in the presence of chemically similar but larger ones, thereby creating substrate selectivity. Next step is to extend this concept to more challenging reactions, finally aiming to tackle the ammonium production problem. Ω

→ **Reference**
P.F. Kuijpers, M. Otte, M. Dürr, I. Ivanovic-Burmazovic, J.N.H. Reek and B. de Bruin, ACS Catalysis 6 (5), 3106-3112 (2016). http://dx.doi.org/10.1021/acscatal.6b00283



↑ **Figure**
The active centre (red/orange) embedded in a supramolecular cage (grey/purple) allows the selective transformation of small molecules in the presence of similar larger ones.

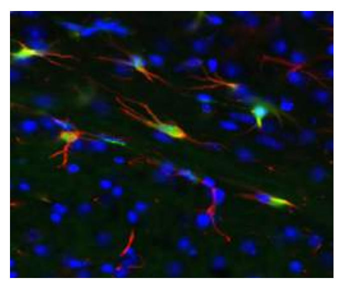
Star-like cells in the brain involved in the fatal 'Vanishing White Matter' brain disorder

STEPHANIE DOOVES is PhD student at the Department of Pediatrics, VUmc.

→ Understanding the underlying mechanism of a disease is an essential part of therapy development. We study a rare genetic brain disorder called 'Vanishing White Matter' (VWM). The brain consists of both 'white' and 'grey' matter. Grey matter contains neurons, which generate the primary processes of thought and movement. Neurons have long protrusions interconnecting them and connecting the brain to the rest of the body for transfer of information. Myelin is an insulating material that is wrapped around neuronal protrusions and is white, thus giving the name to the white matter. Myelin is essential as it enhances speed and efficiency of information transfer, and is made by glial cells of a particular type, known as oligodendrocytes.
White-matter disorders like VWM are traditionally seen as disorders of myelin and oligodendrocytes, in which a lack of or decreased amount of myelin affects the brain's information transfer, leading to loss or hampered brain function such as decreased motor output. From studies on post-mortem brain tissue, we already knew that in VWM not only the oligodendrocytes are impacted, but also another glial cell-type known as astrocytes. These are housekeeping cells in the brain, maintaining normal homeostasis, responding to injury, as well as playing a supporting role to both neurons and oligodendrocytes.

Recently, we developed new mouse models for VWM, in which these mice share the gene mutations of patients. We used a combination of cell cultures of these VWM-mutant mice and post-mortem brain tissue analysis to investigate whether astrocytes or oligodendrocytes are the primary cell type affected in VWM. The data suggested that astrocytic abnormalities precede other disease features like myelin abnormality and motor problems. In VWM mice, astrocytes, which can be detected by expression of the protein glial fibrillary acidic protein (GFAP), also express the protein nestin, which is normally only expressed in immature cells. These astrocytes inhibit the maturation oligodendrocytes by the release of as-yet unknown factors. Recovery of maturation of VWM-mutated oligodendrocytes can be achieved by adding healthy astrocytes to the cell culture, or by adding medium in which healthy astrocytes secreted their factors. A striking new finding was that other, previously unrecognised astrocytic subpopulations are affected in VWM mice and patients as well. Our findings indicate that astrocytes have a central regulatory role in VWM and should receive more attention in the context of the development of VWM therapies. Ω

↓ **Figure**
In the brain of VWM-mutant mice, astrocytes, detected by the protein GFAP (red), express proteins like nestin (green), which is normally expressed only in immature astrocytes.



→ **Reference**
S. Dooves, M. Bugiani, et al. Astrocytes are central in the pathomechanisms of vanishing white matter. J. Clin. Invest. 126, 1512-1524 (2016).

Wobbling whirlpools around black holes

JAKOB VAN DEN EIJNDEN was Master's student Astronomy & Astrophysics at UvA, where he started a PhD project in September 2016.

→ How big is a black hole in the sky when viewed from Earth?? Is it the size of the Moon, a star, or a grain of sand? The answer is that it would look as large as a virus when viewed from a distance equivalent to that from New York to Amsterdam. So how should astronomers, used to observing much larger things, study objects as small as black holes? Surprisingly, music can guide us.

In essence, a black hole is nothing but an object with enough gravitational pull to prevent even light from escaping. As a result, it is impossible to 'see' the black hole itself. However, when a normal star orbits around a black hole its outer layers are stripped off and fall towards the black hole. Just as a spinning top wants to keep spinning, this peeled-off gas keeps rotating and forms a disk – a giant whirlpool with the black hole as its drain. However, although these whirlpools themselves are well understood, it is still being debated how the disk material behaves as it disappears down the drain – where gravity is at its strongest. Zooming in on this process is, due to the size issue mentioned above, an insurmountable task. Therefore, we need another approach to understand what happens right before the gas falls into the black hole.

The music of black holes

Historically, star-swallowing black holes have been studied using two distinct approaches: spectral and timing analysis. In the former, astronomers investigate the observed spectrum: the amount of light received of each wavelength. The observed colour combination gives us a handle on the relevant processes occurring as matter approaches the black hole. For instance, closer to the black hole the material is hotter and emits more light at the blue end of the spectrum. Conceptually, these spectra can be likened to musical chords, just made up of a collection of colours instead of notes of differing frequencies.

Alternatively, timing analysis investigates variations in the brightness of the radiation emitted from the gas travelling towards the black hole. Hence, it tracks how the system changes, from on a slow month-to-month rate, up to swift sub-second timescales. These brightness fluctuations can be considered to represent the rhythm of the whirlpool. While chords and rhythm might be interesting on their own, it is their combination that elevates music to a higher level. Similarly, combining the spectral and timing techniques can increase our knowledge of the behaviour of matter just before it is swallowed by a black hole.

Winding up the whirlpool

Often, the brightness of the gas disk contains fluctuations that are close to, but not perfectly periodic – like a drummer continually just missing the beat. The colours that fluctuate the most originate from the matter closest to the black hole. Hence, these fluctuations provide insight into the matter in extreme gravitational conditions, which is exactly what we want to understand. The variations are thought to be created by *precession* of this very inner part of the whirlpool: as it rotates, it wobbles, causing the brightness observed here on earth to fluctuate. Recently, we have compared the speed of these precessional wobbles, analysing different colours for one specific black hole. This reveals that the material does not precess in unison. Instead, gas close to the black hole precesses faster than gas further out, and as a result the innermost regions get spun up. But just as continuing to wind up a spring, this increasingly spun-up state is unstable and eventually stops the precession. Afterwards, this entire process repeats. This means that instead of peacefully wobbling in a continuous manner, as was thought previously, the rotating gas appears to experience precession in violent spasms just before it falls down the black hole. It was only through combining the rhythm and melody of the emission from the whirlpool of gas that we were able to unravel how matter behaves under such extreme gravitational conditions. Ω

> **"The spectra emitted from matter being swallowed by a black hole are actually quite similar to musical chords, just made up of colours instead of tones."**

↓ **Figure**
Artist's impression of a black hole pulling in the outer layers of an orbiting star. By investigating how this matter circles into the black hole, we can study matter in extreme gravitational conditions (Image credit: NASA).

→ **Reference**
J. van den Eijnden, A. Ingram, and P. Uttley. Probing the origin of quasi-periodic oscillations: the short-timescale evolution of phase lags in GRS 1915+105, *Monthly Notices of the Royal Astronomical Society* 458 (4), 3655 (2016).

An interview with Robert van Langh

Where art and science meet

MICHEL HARING and JOEN HERMANS,
Amsterdam Science magazine editors

→ As you may have noticed in the recent issues of Amsterdam Science magazine, physics and chemistry research is entering the realm of art conservation. To stimulate research in this field, a brand new institute was founded last year: the Netherlands Institute for Conservation Art and Science (NICAS). This institute calls itself a "new innovative interdisciplinary research centre housed in the Ateliergebouw in Amsterdam, uniting art history, conservation and science". Initiated in collaboration with the Netherlands Organisation for Scientific Research (NWO), NICAS will work in cooperation with the Rijksmuseum (RM), the Cultural Heritage Agency of the Netherlands (RCE), the University of Amsterdam (UvA) and Delft University of Technology (TU Delft).

To learn more about the centre and its mission, we set out to meet one of its founders: Head of Conservation and Scientific Research of the Rijksmuseum Amsterdam, and Chair of NICAS, Robert van Langh. It is an exciting opportunity to get into the Ateliergebouw of the Rijksmuseum, the museum's restoration headquarters, as it is an area normally off-limits to regular visitors. We meet Robert in his office, where his windows reveal an inspiring view onto the Rijksmuseum.

How does one become the person responsible for the preservation of one of the largest collections of cultural heritage in the Netherlands?
"I was trained as a goldsmith in Antwerp. I worked for a large jeweller for a while, making good money, but I wasn't sure this was the life for me. One day, a friend asked me «What kind of Porsche are you going to drive?», and I realized I wanted something else. So I went on to study metal and sculpture conservation, and after an internship at the Rijksmuseum as a metal conservator, I slowly climbed the ranks until I was appointed Head of Conservation in 2006."

> **"People start to perceive technical research not as a threat, but as an important tool for understanding works of art."**

Was it important to take a scientific approach when you worked at the metal conservation department in the Rijksmuseum?
"Certainly, it is essential to have a fundamental understanding of the materials you are dealing with. When I worked as a metal conservator at the Rijksmuseum →

20 years ago, the approach to the job was close to «Here's a cloth, go polish the silverware.» That was great in a way, I got to know a large part of the collection. You're polishing Michiel de Ruyter's silver drinking cup, for instance, and realise «Wow, I'm now holding a real piece of tangible history!» But at the same time, I came across so many unanswered questions on the effect of conservation strategies, there was a whole material story behind these objects that I had learned very little about during my training as a conservator. Years later, when I was leading the conservation department at the Rijksmuseum, I realized that being a goldsmith would not be enough for a head of conservation. I had to have a PhD degree in order to have enough authority in the conservation field. We worked together with researchers at the TU Delft at the time, studying phase diagrams of mixtures of metals, and finally in 2006 I was allowed to start my PhD under supervision of Prof. Joris Dik after passing the *colloquium doctum*. I lacked any sort of university education in the natural sciences though - I was taught to think creatively, like one does in art school.

BIO ROBERT VAN LANGH

Born
1968, Oosterhout, the Netherlands.

Study
2006 – 2012, PhD in Materials Science, Delft University of Technology.
Before that, Robert was trained as a goldsmith at the Vrije Technische School 'Technicum' in Antwerp, Belgium, where he also studied Metal Restoration and Conservation at the Higher Institute for Fine Arts.

Work
2006 – now, Head of the Department of Conservation & Restoration of the Rijksmuseum in Amsterdam.
2015 – now, Chairman of the Netherlands Institute for Conservation, Art and Science (NICAS).

What was the topic of your PhD project?
"The project was on neutron imaging of bronze sculptures, and it was an ideal combination of practice and theory. I made bronze reconstructions to get a feeling for the material, analysed sculptures to investigate the material composition and linked the results with art-historical documentation. Basically, I took bronze objects from the collection of the Rijksmuseum to the neutron source in Switzerland for imaging, creating something similar to an X-ray photograph of the sculptures. With those images, you can see differences in density of the metal, and find out where the surface has been worked with a hammer after casting. The objects become slightly radioactive in the process, so we had to leave them in a safe in Switzerland for three weeks to 'cool down', so to speak. But every time we took an object for neutron imaging, we got interesting results. Connecting results from analyses and historical research, it became clear that it wasn't the world-famous Benvenuto Cellini in Florence who was the first to cast bronze in incredible detail without the need of hammering the surface, but that German artists in Nuremberg had already optimised this technique forty years earlier."

Do you experience any difficulties in bridging this gap between the arts and the natural sciences?
"When I first presented our results on the bronze sculptures, I was met with a lot of scepticism. You cannot simply come in with your measurements and conclusions, and expect connoisseurs to be convinced. Forget it, they won't believe it. I needed to turn my message around, show my measurements and ask «Can you give an explanation for what I am measuring?» In the art world, it is still very much the opinion of leading experts that is valued most; when the Cellini expert says no, it is no. Trying to change that culture with scientific research is an interesting challenge of which the final step may take another generation or so. Yet, it does change. People start to perceive technical research not as a threat, but as an important tool for understanding works of art."

Is there a role for NICAS in this respect? Are there many other places around the world where scientists, conservators and art historians really work together?
"NICAS is definitely a step in the right direction. Amsterdam is one of the very few places where there is such a good mix of disciplines. Maybe the Getty in Los Angeles (http://www.getty.edu/), the Art Institute of Chicago in collaboration with Northwestern University or the Doerner Institut in Munich (http://www.doernerinstitut.de/) have a comparable approach, but NICAS has it all. In many museums, the head of conservation is still completely subordinate to the curator of the collection and has to follow his orders. In the Rijksmuseum, we try to level this out and give everyone an equal voice when deciding how to treat an object. Only when curators and conservators collaborate as equals the potential of conservation and scientific research can be fully developed. Ideally, NICAS should be just the start of a bigger research effort to understand the state of our cultural heritage. We want to know: how was it made, what state of degradation are we dealing with, which new diagnostic tools can we develop and how long will it last? After all, how old will Rembrandt's Night Watch be before it's beyond recognition? We need this knowledge to conserve our artworks for as long as possible."

We have clearly hit on a sensitive subject, as Robert continues with great passion:
"What I really don't understand, not for one bit, is why there is no greater investment in the preservation of cultural heritage. The 5 million euro we got from NWO when NICAS was founded is very nice, but realistically, it's a drop in the ocean. Everyone seems to agree it is very important to maintain our historical record, but we have no idea what kinds of degradation are affecting our collections as we speak. It is a cumulative effect, objects are fading all the time. Are we still looking at the original colour on a Rothko painting? Nobody can tell you. If you look at a typical 30-year-old photograph, it has yellowed entirely. Your favourite shirt probably has rips and tears after a few years, because textiles wear down. I see it as my mission to create awareness in our society that art and cultural heritage are temporary. Solutions to preserve objects for a long time are definitely possible, but to do so we need high-quality research and permanent funding. Sometimes I say, not entirely seriously, that we should stop treating objects altogether for a generation or so and direct all our efforts and funding to research so we can make some good progress. There is a lot of low-hanging fruit, problems in conservation of cultural heritage objects that are not incredibly hard to solve with the current state of knowledge in the natural sciences, and a lot of art historical information can be obtained with established analysis techniques. There is so much knowledge readily available both at universities and in industry about materials and degradation processes, and I see a lot of willingness to help in those places. It even works the other way around: researchers at AkzoNobel who work with modern paints were very interested to learn about our experiences with paint degradation. The only thing we need to do is connect groups of people that already share this common interest and create the means for them to work together."

What has been your own role in bringing all these people together for conservation research?
"I am not important. A group of motivated people has been material to the formation of NICAS. Now that we have a starting point, the challenge is to consolidate and formalise its position. We need long-term investments so this research becomes more that just isolated projects, it should become a permanent programme. The work should continue without individuals like me."

When browsing through the website of NICAS (http://www.nicas-research.nl/) it is clear that a wealth of projects is underway. Several projects study ageing processes in oil paints, while others try to develop better tools to investigate how different artefacts have been made. In addition to research, NICAS is also a boost for the Master's programme Conservation and Restoration of Cultural Heritage of the Faculty of Humanities of UvA. At the moment, around forty students are enrolled in this programme, all benefitting from the dynamic collaboration between the NICAS partners. Robert explains: "It is also very important that we provide a place for young researchers, Master's degree students, PhD students and postdocs, from the conservation field as well as the natural sciences, to develop themselves as experts and then out into the wider world: we received a grant from the National Science Foundation (the counterpart of NWO in the US) to send top American students to NICAS, and we have collaborations with the Getty and the Metropolitan Museum in the US and contacts elsewhere, we can send them anywhere. This thing must grow and grow!"

"I see it as my mission to create awareness in our society that art and cultural heritage are temporary."

What are the future developments within NICAS that hold great promise?
"One of the developments that hold great promise is the involvement of data science in the analysis and organisation of collections. So many collections worldwide are not completely open to the public. By creating digital databases, all art becomes available to the public and the scientific community."

Using image-recognition software, styles of artists or art periods can be unravelled. One of the ongoing projects aims to revive the study of stylistic development of painting by developing a visual analytics framework combining subjective connoisseurship with computer learning. In addition, stronger support for identification of the original artist can be generated using computer-based algorithms." Robert refers to the research of Prof. Robert G. Erdmann (UvA), who contributed strongly to the Bosch project (http://boschproject.org/), as an example of the use of high-resolution analytical photography/spectroscopy to investigate the technical aspects of the paintings of Jheronimus Bosch.

Finally, Robert returns to a point that keeps coming back in our conversation. "I need to reach out to the public, seek publicity, make movies about what we do, to raise money for this research. Why not 20 million euro over 10 years, to preserve a record of our past. How much is that on a government's budget? This is what I need to do; send this message into the world, until the public simply asks «Why are we not funding this?»" Ω

Conserving oil paintings: a soap story

JOEN HERMANS is PhD student in chemistry/conservation science at the Van 't Hoff Institute for Molecular Sciences (HIMS), UvA.

→ Oil paintings are not stable objects, when looking from a thermodynamic point of view. When oil paint dries, the oil medium in which the pigment particles are suspended polymerises, leading to a complex heterogeneous system where pigment particles (usually metal salts) can still react with their polymer surroundings. Even after an initial drying stage, slow chemical and physical processes may change the way a painting looks and determine how sensitive it is to cleaning or transport.

One of the major concerns for paintings conservators is the formation of so-called 'metal soaps'. When these complexes of metal ions and fatty acids start accumulating inside a layer of paint, they can lead to clearly visible spots on the surface of a painting (see Figure), or cause entire paint layers to crumble or become transparent. The problem is worryingly common, with an estimated 70% of museum collections worldwide showing signs of metal soap-related degradation. Despite the scope of the metal soap issue, we are only recently starting to understand how metal soaps are actually formed from this complex mixture of pigment and oil polymer.

Previous research found out that lead and zinc, present in the most common white pigments, are the main culprits in forming big metal soap aggregates. We have also learned that the fatty acids are released from the oil polymer through a reaction that involves water. At the same time, the metal ions can spread from the surface of pigments into their environment by binding to charged groups on the oil polymer. Understanding these processes gives us some ideas about how we should store and treat paintings to minimise these early stages of degradation. However, in many paintings, the formation of metal soaps has already begun. Therefore, we have also studied later stages of degradation, to find out why the amorphous complexes of metal ions and fatty acids start to crystallise, accumulate and form big, disturbing aggregates.

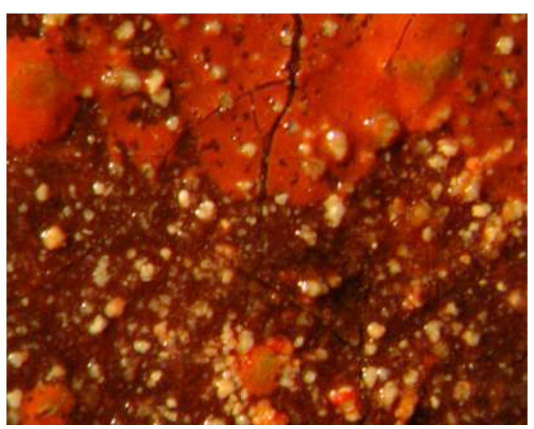
Starting with relatively simple model systems of metal soaps in liquid oil at a range of concentrations, we measured the temperature at which rapid metal-soap crystallisation starts as function of concentration. With that information, it became clear that the reason for widespread metal soap crystallisation is simply that the solubility of metal soaps in oil is extremely low. In other words, as soon as metal ions start binding to fatty acids, the system becomes unstable and tends to show metal-soap crystallisation. This crystallisation is a spontaneous and irreversible process, which is quite problematic when trying to conserve oil paintings. A second important experimental finding was that the rate of crystallisation is very sensitive to the properties of the oil. As the oil became more viscous and polymerised during drying, metal soap crystallisation slowed down dramatically or stopped entirely. Additionally, the two most common metal ions involved in metal soap formation, lead and zinc, had very different crystallisation rates. This finding helped explaining why lead and zinc soaps often appear with quite different morphologies in oil paint films. Though slow processes can be difficult for research purposes, it is good news for the conservation of oil paintings that metal soap crystallisation is so slow in fully dried paint. We might not

"We hope to provide the oil-paint conservation community with a better chemical basis for improved cleaning strategies."

be able to prevent metal soap molecules from forming, but it might be possible to minimise the chance of starting metal soap crystallisation or the large-scale growth of metal soap crystals. For example, oil paintings often come into contact with a range of polar and apolar solvents during cleaning and restoration. Also, in the past many paintings have been briefly heated with irons when a new stretch of canvas needed to be attached to the back of paintings for support. Such treatments have been necessary to keep the oil paint and canvases in good condition. Nevertheless, they also soften the oil paint and increase the mobility of molecules involved in metal soap crystallisation. We are now focusing on studying how fast different cleaning solvents diffuse into oil paint layers and how each influences the crystallisation rate of metal soaps. By doing so, even though metal soap crystallisation can't be prevented entirely, we hope to provide the oil paint conservation community with a better chemical basis for improved cleaning strategies. Ω

→ **References**

1. J.J. Hermans, K. Keune, A. van Loon and P.D. Iedema, An infrared spectroscopic study of the nature of zinc carboxylates in oil paintings. J. Anal. Atom. Spectrom. 30, 1600-1608 (2015).
2. J.J. Hermans, K. Keune, A. van Loon and P.D. Iedema, The crystallization of metal soaps and fatty acids in oil paint model systems. Phys. Chem. Chem. Phys. 18, 10896-10905 (2016). http://dx.doi.org/10.1039/C5JA00120J http://dx.doi.org/10.1039/C6CP00487C



→ **Figure**
Johannes Vermeer, View on Delft, 1660-61, oil on canvas, Mauritshuis, The Hague, with a microscope image clearly showing the formation of white lumps of lead soaps. Overall image courtesy of the Mauritshuis. Detail photograph by A. van Loon, Mauritshuis.

From mendelian inheritance to the petunia genome

MARIA CONSTANTIN is PhD researcher at the Swammerdam Institute for Life Sciences (SILS), UvA.
MICHEL HARING is Professor of Plant Physiology, UvA.

→ **Figure**
1. Petunia collection in the greenhouse of the Faculty of Science, UvA (image credit: Jan van Arkel, IBED, UvA).
2. Palm Greenhouse (built in 1912) in de Hortus Botanicus Amsterdam (image credit: unknown).

→ 150 years ago, Mendel first communicated his ideas about the heritability of plant traits. His paper 'Versuche über Pflanzenhybriden' (*Experiments on Plant Hybridisation*), which was presented in 1865, remained largely unnoticed until early in the 1900s scientists rediscovered his work. One of them was the Amsterdam scientist Hugo de Vries, professor of Plant Physiology, who worked on the heritability of traits in plant species, mainly the evening primrose. De Vries was the first to introduce the term 'genes' for units of heritability. He did his research at the Amsterdam Hortus Botanicus which still carries the name 'Hugo de Vries Laboratory'. Genetics research at the University of Amsterdam was re-introduced in the late 1950s when petunia was chosen as a model system to study the genetics of flower colour and shape. In that period, the group of Professor Frans Bianchi collected many different petunia varieties from all over the world. His research group maintained this collection and added the new varieties flowering in their greenhouses. This resulted in a large collection of petunia hybrids and mutants that has allowed the dissection of the genetic pathway for flower colour formation.

In the mid-eighties, the petunia collection moved to the VU University, where research entered the age of gene identification and genetic modification. The genetic research on petunia now bloomed in the southern part of Amsterdam. The most striking highlight was the discovery of gene silencing by antisense RNA, nicely illustrated by the loss of flower colour in a seminal *Nature* paper [1]. The Amsterdam expertise on flower colour, plant architecture and floral scent fully originated from studies on this elegant model plant species. In 2015, the petunia collection - now consisting of more than two hundred different lines and wild varieties - returned home to the greenhouse of UvA, now at the Science Park (see accompanying image).

This year, a consortium of petunia researchers published the genome sequence of the wild petunia and illustrated how the garden variety we all know came into being through hybridisation [2]. This paper also highlighted that petunia has always been a showcase for 'jumping genes' (also known as transposons), nicely visible as coloured spots on a white petal background (see cover image of this issue). In the white areas of the flower, a gene for flower colour formation has been disrupted by the insertion of the transposon. If this transposon 'jumps' out again, flower colour biosynthesis is restored and cells, or even larger parts of the tissue, regain their characteristic red colour. The identification of the active transposon has resulted in a controllable, natural, mutation machine that has since allowed the discovery of many genes involved in determining flower colour and shape. The genome of the two parents of the hybrid bedding plant revealed that both wild petunia species indeed contributed to the major part of the genetic information that we find in modern garden petunia. However, at least for the hybrid lines analysed so far, the contribution of the white flowering *Petunia axillaris*, seems to be strongest (15,000 genes vs. 600 from Petunia inflata). Despite the detailed information we now have on the family tree of the petunia, it was also found that 2000 genes originate from an as-yet-unknown ancestor. In addition, rather than inheriting the genes for a particular trait from either one or the other parent, as many as 1500 genes seem to be hybrids of genes from both parents. These unusual 'hybrid genes' might have originated from special recombination events between the two genomes.

Based on Gregor Mendel's 150-year-old concept of heritability and the use of directed crosses, work has moved on from the use of a genetic model system some fifty years ago to the present-day era of genome sequencing and detailed dissection of genetic mechanisms, an endeavour in which our Amsterdam research stands out proudly! Ω

→ **References**

1. A.R. van der Krol, P.E. Lenting, J. Veenstra, I.M. van der Meer, A.G.M. Gerats, J.N.M. Mol and A.R. Stuitje, An antisense chalcone synthase gene in transgenic plants inhibits flower pigmentation. Nature 333, 866-869 (1988).
2. A. Bombarely et al. Insight into the evolution of the Solanaceae from the parental genomes of Petunia hybrida. Nat. Plants 2 (6), 16074 (2016).

Accelerating medical knowledge exploitation

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MOHAMMAD SHAFAHI, PhD Student at the Informatics Institute, UvA.

→ In 2015, according to the World Health Organization (WHO), 39.2 million people died due to non-communicable diseases, two thirds of the total deaths that year due to a cause. WHO predicts this number will increase to 51.8 million by 2030, three-quarters of the total deaths due to a cause. These growth figures easily outstrip population growth and illustrate the challenge we face to correctly diagnose and effectively treat disease. Fortunately, medical research continuously comes up with new discoveries and trial results, but unfortunately, only part of this information finds its way to the patient or her/his doctor. For example, the MEDLINE database currently contains over 23 million publications, more than over 806,000 of which were added in 2015 alone. Why isn't all this research helping to improve things in practise? One reason could be the current way official medical guidelines are developed. These summarize the existing literature for practitioners, assisting in assessing patients' health and recommending possible treatment pathways, however their current development involves manual searches through vast amounts of disease-related scientific publications. Given the explosive growth of MEDLINE, this has become highly ineffective and an updated version of a medical guideline can take half a decade to produce! To speed things up, it is therefore imperative to develop semi-automated systems.

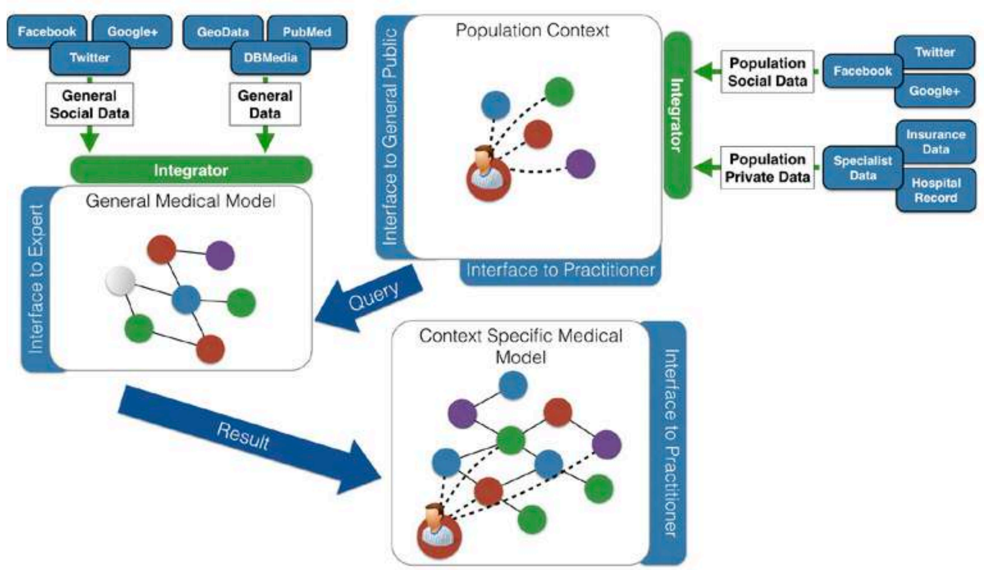
Not only doctors and health professionals, but also the general public can benefit from more up-to-date awareness and insight about diseases. To better tap into the vast amount of existing medical knowledge and make it available to different stakeholders, and to reduce the time/cost of making the public more health-aware, we have developed the ODMA (Online Dynamic Medical Assistant). This smart system gathers, clusters, integrates, and customizes knowledge about diseases and risk factors, and identifies their semantic inter-relationships. It encompasses a variety of existing, statistically verified authoritative digital sources, including research publications, health articles, medical guidelines, and meta-models for diseases and their risk factors developed by experts (see Figure). In addition, ODMA can be customized using individual patient data, or further interlinked with unobtrusively collected contextual information about certain target populations' health and daily habits, through the social media and news outlets.

ODMA utilizes and represents the medical domain data in a graph, consisting of all concepts and relationships among them, using the standardized ontology of the unified medical language system. ODMA's primary knowledge base captures the medical peer-reviewed literature from several large data sources, and exploits "Linked Data" technologies to deal with large amounts of heterogeneous and dynamic information. It is designed to both scale up and scale out, and at present uses the SurfSara's high performance computing cloud infrastructure to gather, process, and analyse all the information.

Our group were the first to develop a user-friendly graphical Explore-Interface tool, to support researchers in exploring medical information and linking to disease models. Semantic-based querying and ranking of relevant sources is also supported, assisting the validation of new hypotheses against peer research, for example when extending a disease meta-model with new risk factors or new medication strategies.

The latest developments include social bots which interact with target populations via social media, in order to raise health awareness. Tweets can provide people with key points from scientific articles chosen to be relevant to the context of each audience group. In addition, customized recommendations can be provided to individuals who voluntarily provide their personal health data, through personal channels such as Facebook messenger.

ODMA is set to play a key role in using the huge (bio)medical research knowledge so as to improve everyday healthcare practice and public awareness, and reduce the otherwise growing impact of disease on our life quality and expectancy. Ω



↘ **Figure**
Architecture of the Online Dynamic Medical Assistant (ODMA).

→ **References**
1. Shafahi, M., Bart, H., & Afsarmanesh, H. (2016, February). Biomed Xplorer - Exploring (bio)medical knowledge using linked data. In Proceedings of the 9th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2016).
2. Shafahi, M., Hu, Q., Afsarmanesh, H., Huang, Z., ten Teije, A., & van Harmelen, F. (2016, May). A Task-based Comparison of Linguistic and Semantic Document Retrieval Methods in the Medical Domain. In Proceedings of 1st Workshop International Workshop on Extraction and Processing of Rich Semantics from Medical Texts at ECSW.

Powerhouse at the centre of the Milky Way

↗ **Figure**
Artist's impression of what happens in the centre of our galaxy. The supermassive black hole accelerates protons (the blue spheres) to very high energies. These then interact with particles in the giant molecular clouds surrounding the galactic centre, emitting gamma rays (the yellow waves). These gamma rays fly in straight lines, so we can determine where they came from. © Dr. Mark A. Garlick/H.E.S.S. Collaboration

→ An international team of scientists, united in the H.E.S.S. collaboration and including researchers of UvA's Anton Pannekoek Institute for Astronomy and Institute of Physics, has mapped the region around the centre of our galaxy using very-high-energy gamma rays. Detailed analysis of these data reveals for the first time a source of cosmic radiation in our galaxy at energies never observed before. As reported in *Nature* on 16 March, the researchers suspect that the supermassive black hole at the centre of the Milky Way is the culprit.

The Earth is constantly bombarded by high-energy particles (protons, electrons and atomic nuclei) of cosmic origin, particles that comprise what is called cosmic radiation. These cosmic rays are electrically charged, and are hence strongly deflected by the interstellar magnetic fields that pervade our galaxy. Their paths through the cosmos to our telescopes are randomised by these deflections, making it impossible for us to directly identify where they come from. Thus, more than a century since the discovery of cosmic rays, their origin remains one of the most enduring mysteries of science.

Fortunately, cosmic rays also interact with gas in the neighbourhood of their sources, producing gamma rays. Gamma rays are photons, and as such they travel in straight lines, unimpeded by magnetic fields. As these gamma rays can be traced back to their origin, they can be the key to uncovering the source of those enormously energetic charged particles that bombard the Earth.

When a very-high-energy gamma ray reaches the Earth, it interacts with molecules in the upper atmosphere, producing what we call a 'shower' of secondary particles, and these emit a short pulse of Cherenkov radiation (more commonly known from the eerie blue glow seen in the core of nuclear reactors). The Cherenkov radiation from the shower can be detected on Earth using arrays of telescopes equipped with large mirrors, sensitive photo-detectors and fast electronics. The H.E.S.S. (High Energy Stereoscopic System) observatory in Namibia is leading the field as the latest generation of such telescope arrays. More than 100 sources of very-high-energy gamma rays have been identified over the past decade by these telescopes.

We know that cosmic rays with energies up to approximately 100 teraelectronvolt (TeV, 1012 eV) are produced in our galaxy by objects such as supernova (star explosion) remnants, compact clusters of massive stars, and pulsar wind nebulae such as the well-known Crab nebula. To put this into perspective, a TeV is around the energy of a flying mosquito. Put all this energy into a single proton, such as is done at the Large Hadron Collider at CERN, or as done >100 times in cosmic rays, and it'll pack quite a punch. Both theoretical arguments and direct measurements of cosmic rays on Earth indicate, however, that the cosmic-ray factories in our galaxy should be able to provide particles up to at least one petaelectronvolt (PeV, 1015 eV), and the field was waiting with bated breath for the first galactic particle accelerator to break through the PeV barrier.

> **"The field was waiting for the first galactic particle accelerator to break through the peta-electronvolt barrier."**

During the first three years of observations, H.E.S.S. uncovered a very powerful point-source of gamma rays in the galactic-centre region. The coincidence of this gamma ray-rich region with regions of enhanced density in the giant molecular clouds around the galactic centre indicated the presence of one or more accelerators of cosmic rays in that region. However, the nature of the source remained a mystery.

More recent and deeper observations obtained by H.E.S.S. between 2004 and 2013 revealed spectacular news: somewhere within the central 33-light-year-large core of the Milky Way, there is an astrophysical source capable of accelerating protons to energies of about one PeV, continuously, over a time-scale of at least 1,000 years.

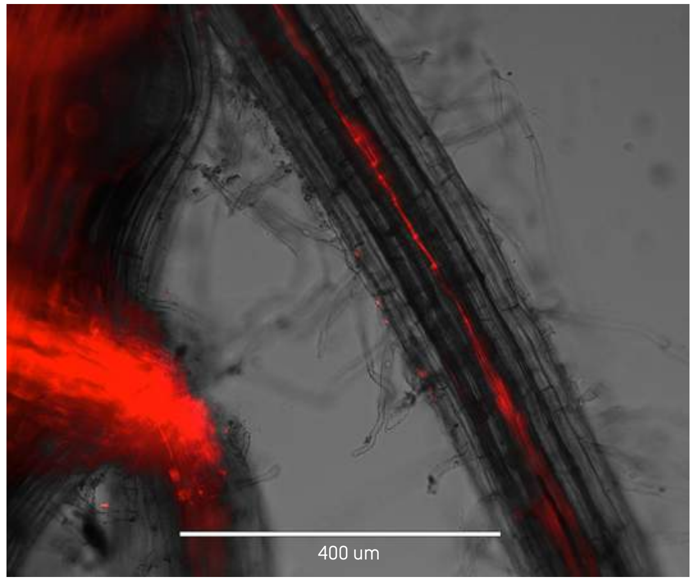
So what is this turbo-charged particle accelerator at the core of our galaxy? The galactic centre is home to many objects capable of producing cosmic rays of high energy. According to the H.E.S.S. scientists, however, the most plausible source of the PeV protons is the supermassive black hole located at the centre of the galaxy, which goes under the rather cryptic name Sgr A*. Several possible acceleration regions are under consideration, either close to the event horizon of the black hole, or farther away from it. Although there still remains much work to be done, such as understanding the discrepancy between the number of high-energy galactic particles and the total flux of cosmic rays detected on Earth, these new data mark a milestone in demystifying the source of the highest-energy galactic particles humanity has ever measured. Ω

→ **Reference**
H.E.S.S. Collaboration, corresponding authors: F. Aharonian, S. Gabici, E. Moulin and A. Viana, Acceleration of petaelectronvolt protons in the Galactic Centre, Nature 531, 476-479 (2016).

H.E.S.S. home page:
www.mpi-hd.mpg.de/hfm/HESS/

Sharing is caring: how non-sexual fungi share information and create diversity

IDO VLAARDINGERBROEK performed his doctoral research in the section of Molecular Plant Pathology at the Swammerdam Institute for Life Sciences, UvA.



↙ Figure
The fungus Fusarium oxysporum can be seen growing inside a tomato root cell. In this way the fungus can feed on the sugars from the plant. The fungus produces a red fluorescent protein, allowing it to be easily visualised in plant tissue.

→ While sex is a great driver of evolution by creating diversity, many species have to do without it. One of these poor creatures is our favourite fungus *Fusarium oxysporum*, a pathogen that is able to colonise the roots of many different plant species (i.e. tomato, cucumber, melon and banana, see Figure). By doing so, it causes wilting of the plant. However, in the case of filamentous fungi like *Fusarium* there are often alternatives to create genetic diversity. The genome of *F. oxysporum* appears to consist of two separate 'compartments'. The first compartment, known as the core genome, takes care of the cell maintenance, and encodes instructions on how to feed, grow and replicate. Next to this core part of the genome, there is a lineage-specific (LS) part; this part is highly variable between different closely related species and even between different strains of the same species. The LS part of the genome contains unique information, which in the case of *F. oxysporum* is required to cause disease in tomato plants. In the tomato-infecting strain, our object of study, the LS part of the genome consists of several chromosomes. We discovered that one of the small LS chromosomes, chromosome 14, which carries a set of genes essential for infection of plants, can be exchanged between strains in a non-sexual way.

Subsequently, we wanted to find out if other, larger LS chromosomes and perhaps even regions of the core genome are exchangeable between strains. The main question was: what distinguishes chromosomes that can be transferred from those that cannot? We approached this problem by incorporating an antibiotic resistance gene in selected chromosomes. If these chromosomes are transferred to a recipient, the strain will become resistant. We also randomly inserted the antibiotic resistance gene into the genome. In strains that had received a chromosome we could then determine the identity of the transferred chromosome. By sequencing the whole genome of these novel strains we could exactly determine which genetic information was obtained from the donor strain. At first, all our results pointed to the same conclusion: transfer of chromosome 14 only, as described previously. However, careful analysis of the genome sequence of the recipient revealed unexpected results. While chromosome 14 was transferred in all strains recovered, it was not the only chromosome transferred. In two cases we discovered that core chromosomes, containing the antibiotic resistance gene, were transferred first, and the LS chromosomes simply hitchhiked along. Since the two strains we used are very closely related, the information on these core chromosomes was already present. By looking for small differences in the genome sequences we were able to determine which parts originated from the donor strain. Interestingly, the corresponding region of the receiving strain was lost after uptake of the core chromosome: gene conversion.

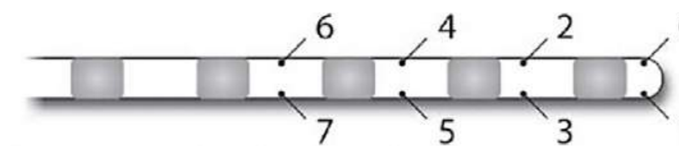
> **"Much larger chromosomes than previously observed can be transferred in a non-sexual way."**

It seems we discovered a process that is rare, and has little impact on growth and development of the fungus, or its ability to infect a host. Even so, we were able to draw some important conclusions from our observations. First of all, we show transfer between fungal strains is not restricted to LS chromosomes, which means that no special structure is required for transfer. Secondly we show much larger chromosomes than previously observed can be transferred. And finally we show chromosomes often migrate together. Our results do further strengthen the idea that asexual fungi exchange information more readily than was previously thought. Apart from the transfer described above, we were also able to determine that regions of the genome can be lost spontaneously or duplicated. It appears that in absence of a sexual cycle other methods of creating variation have evolved. Previously, these non-sexual lineages were seen by some as 'evolutionary dead ends'; strains adapted to the current situation, but no longer able to respond to changes. As is often the case, nature appears to be more resourceful than that. These fungi turn out to have a highly variable genome, allowing them to quickly adapt to changes in demands placed by the plant host and its environment. Ω

→ Reference
I. Vlaardingerbroek, B. Beerens, L. Rose, L. Fokkens, B.J.C. Cornelissen and M. Rep, Exchange of core chromosomes and horizontal transfer of lineage-specific chromosomes in Fusarium oxysporum. Environ Microbiol. (2016) http://onlinelibrary.wiley.com/doi/10.1111/1462-2920.13281/abstract

Visual brain cells think too

JESSY POSSEL is PhD student at the Department of Vision and Cognition, Netherlands Institute for Neuroscience.



← Figure
The electrode used to measure brain activity has a diameter of 1.2 mm. The grey sites (contacts) are used to record brain activity of a group of cells around the contact to determine the location of the epilepsy. The small wires at the side and end of the electrode allow to record the activity of single cells in the brain.

→ To get insight in how the brain functions, the golden standard is to measure the activity of single cells. However, opportunities to record activity from cells inside the human brain are very rare and only occur under certain unique circumstances, for example during brain surgery. Another unique opportunity in which brain activity of single cells can be measured is in some epilepsy patients that need extensive monitoring of their brain signals as a part of their treatment. In these patients, surgeons at the Vrije Universiteit Medical Centre (VUmc) implant electrodes in multiple brain areas. With these electrodes, brain activity is continuously measured for a period of one to two weeks, so that the onset and location of seizures can be precisely determined.

The Netherlands Institute for Neuroscience collaborates with VUmc to make use of the exciting opportunity to record signals from single cells in the human brain. Patients are asked to perform simple tasks on a computer screen while their brain activity is recorded. This way we can explore what happens inside the brain when, for example, a patient remembers an item or pays attention to a given object. For this research, special electrodes are used that have small wires either along the sides of the electrode or at the tip. These wires make it possible to record brain activity from single cells.

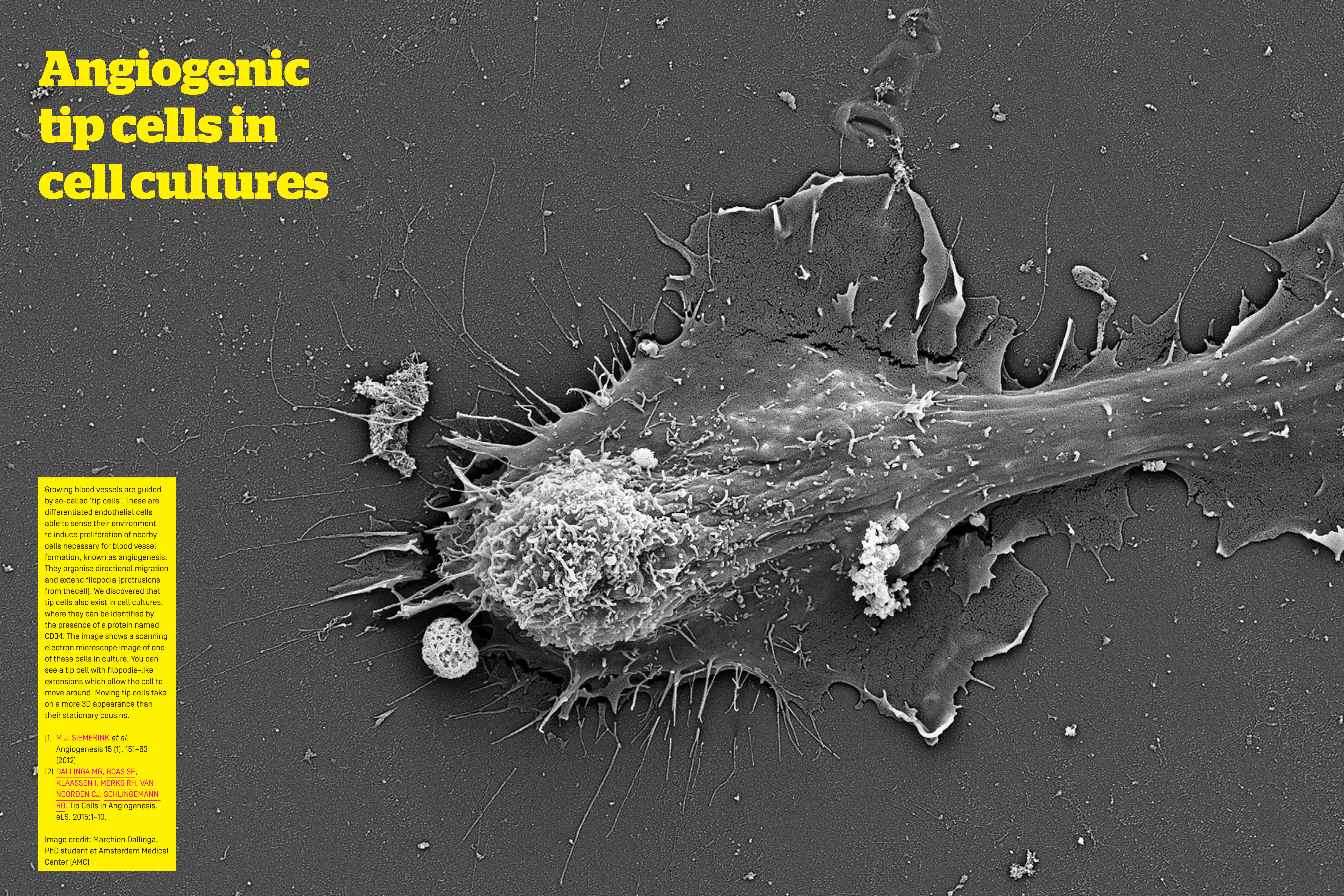
The source of the epilepsy is often located in the medial temporal lobe, which is a part of the brain that is involved in memory and emotion. Therefore, electrodes are often placed in the medial temporal lobe. However, the location of the implanted electrodes is individually determined for each patient, based on their unique clinical characteristics.

Recently, an epilepsy patient was implanted with an electrode in the visual cortex; this is very unusual as the visual cortex is rarely involved in epilepsy. The visual cortex is responsible for processing what we see. Our knowledge of how the cells in the visual cortex work is largely based on studies on animals (such as cats, macaque monkeys and mice) in which electrical activity has been directly recorded from the brain. In 1959, Hubel and Wiesel discovered that cells in the visual cortex respond to stimuli in a certain location of the visual field; this is called the receptive field of the cell. When something is presented elsewhere (outside its receptive field) the cell is quiet. One single cell only sees what happens inside its receptive field and is blind to the rest of the visual field. The combined 'images' of all individual cells give us the full picture. We recorded brain activity in the visual cortex while the patient looked at images on a computer screen. We presented stimuli on different locations on the screen and located the receptive field of the cells. The patient's brain cells increased their firing rate in response to simple image properties, such as the contrast of an object or the direction in which an object moved. The response of the cells was also increased for visual objects relative to backgrounds, even when what the cell 'saw' in its receptive field was identical. This finding is an important step in understanding how the brain segments objects from their background. The timing of this effect indicates that the segmentation of an object from the background might happen first in higher order visual (brain) areas and is then fed back to early visual areas.

For humans, current data on whether the activity of these brain cells is influenced by thought processes like attention present a mixed picture. We showed that when the patient attended to an object in the visual scene, the neural representation of that object was strengthened, whereas the representation of other irrelevant objects was weakened. This discovery offers new insights into the way the human brain thinks about a visual image and demonstrates that the human visual cortex has very similar properties to the visual cortices of other animals such as macaque monkeys or mice. Therefore, these animals are a useful model for the human visual cortex. We have published these exciting findings in an article in *PLoS Biology* on 25 March 2016. Ω

→ Reference
M.W. Self, J.C. Peters, J.K. Possel, et al. The Effects of Context and Attention on Spiking Activity in Human Early Visual Cortex. PLoS Biol 14 (3) e1002420 (2016)

Angiogenic tip cells in cell cultures



Growing blood vessels are guided by so-called 'tip cells'. These are differentiated endothelial cells able to sense their environment to induce proliferation of nearby cells necessary for blood vessel formation, known as angiogenesis. They organise directional migration and extend filopodia (protrusions from thecell). We discovered that tip cells also exist in cell cultures, where they can be identified by the presence of a protein named CD34. The image shows a scanning electron microscope image of one of these cells in culture. You can see a tip cell with filopodia-like extensions which allow the cell to move around. Moving tip cells take on a more 3D appearance than their stationary cousins.

[1] M.J. SIEMERINK *et al.* Angiogenesis 15 (1), 151–63 (2012)

[2] DALLINGA MG, BOAS SE, KLAASSEN I, MERKS RH, VAN NOORDEN CJ, SCHLINGEMANN RO. Tip Cells in Angiogenesis. eLS. 2015;1–10.

Image credit: Marchien Dallinga, PhD student at Amsterdam Medical Center (AMC)

Proteins in transition: a Petri net model for cellular signalling

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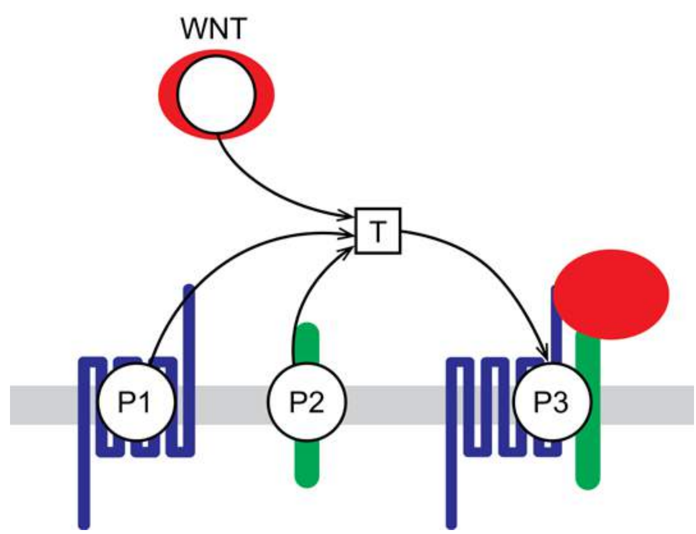
ANNIKA JACOBSEN is PhD student in the Centre for Integrative Bioinformatics (IBIVU), VU.

→ At the molecular level, all cell behaviour is controlled by complex networks of interacting proteins. Understanding how these so-called signalling pathways function is challenging but also crucial to curing diseases caused by deregulated signalling, such as cancer. Computational models can help to improve our understanding of complex and dynamic signalling events, but despite their complexity they can only describe a small part of the signalling network. Petri net models offer an intuitive, graphical representation of these kinds of networks.

A Petri net is composed of 'places' describing biological components and 'transitions' describing interactions between the biological components, which are connected with 'arcs'. The places can contain 'tokens' that represent the relative protein levels. The arcs have weights representing the consumption/production of the tokens. When simulating a Petri net model, the transitions transfer tokens between the places in a step-wise manner. At the end of a simulation, the amount of tokens in the places are different, and these changes represent the dynamic behaviour being modelled. By combining wet-lab (experimental) and dry-lab (computational) approaches, collaborators at VU and UvA have begun to decipher the so-called Wnt/β-catenin signalling pathway. This pathway is vital for the proper development of all multicellular animals, and its deregulation can cause a range of diseases, including cancer. In a recent publication in *PLoS ONE*, Jacobsen and colleagues describe how they successfully constructed and experimentally validated a Petri net model of the core Wnt/ß-catenin pathway. The simulations predict the response of the pathway upon supra-physiological (e.g., oncogenic) activity, compared to normal signalling (e.g., during development). This experimentally tested Petri net model can now be extended to include additional components, so as to be able to describe more complex signalling behaviour. Ultimately, cross-talk with other signalling pathways - which could lie at the root of deregulation - can be simulated and predicted. Ω

→ Reference
A. Jacobsen, N. Heijmans, F. Verkaar, M.J. Smit, J. Heringa, R. van Amerongen and K.A. Feenstra, Construction and Experimental Validation of a Petri Net Model of Wnt/β Catenin Signaling. PLoS ONE 11 (5), e0155743 (2016)



→ Figure
Close-up of a part of the Petri net model. Each protein or protein complex is defined as a place (P). The transition (T) represents the formation of the complex.

To Open Access or not to Open Access?

JEAN-SÉBASTIEN CAUX is Professor in Theoretical Condensed Matter Physics at the Institute of Physics (IoP), UvA.

→ Open Access is currently a hot topic of discussion, from your local institution's coffee corner to international-level meetings. With the recent Amsterdam Call for Action on Open Science [1] (building up on the earlier Budapest [2], Bethesda [3] and Berlin [4] statements) for all publicly funded research output to be Open Access by 2020, it seems that authorities are taking good care of us researchers and that all plans are set for the needed transition away from paywall-protected publishing. But from the vantage point of a practising scientist, is all as rosy as it seems?

Let us first recall the definition of the term `Open Access' [5]. Primarily, it means that readers can view publications without subscription or per-paper charges. In the `gold' version, authors pay a one-time fee to publishers, typically ranging from around a thousand euros to many times that, in order for the article to be freely downloadable. In the `green' version, authors instead put a version of their paper in an openly-accessible repository (institutional, or as a preprint on repositories like arXiv.org), with restrictions (e.g. embargo period) imposed by the publisher. The concept of Open Access also covers reuse rights of the work: users must ideally be able to `copy, use, distribute, transmit and display the work publicly and to make and distribute derivative works, in any digital medium for any responsible purpose, subject to proper attribution of authorship' [3,4]. Although the recent developments are obviously welcome, if you were tasked with designing a publication system from scratch, is this really what you would come up with? Let us for a moment toy with the idea of designing such a system starting from the interests of professional researchers, and aiming to best serve the interests of science itself, in the true age-old spirit of openness among the scientific community. What would you advocate?

- Of course, there should be no paywall for viewing publications: the traditional business model can seemingly only exist in academia [6]. The status quo must clearly disappear in favour of publications that are openly accessible to all interested parties, from the specialist to the curious teenager in a developing country, without forgetting the smart data-mining robot;
- Going one step further than current definitions of Open Access, there should also be no paywall for publishing (`two-way open access'). Many scientists are lukewarm or downright hostile to the idea that authors should carry the costs of publishing (not to mention the unwelcome additional administrative burden of funding and processing this payment). A better system would see these costs minimised by publishers and covered directly by the funding agencies;
- Reuse of published works must be permitted under appropriate attribution, this being best implemented via a Creative Commons or similar license (e.g. CC-BY). Authors should also be the copyright owners of their work, as happens in normal walks of life;
- In fact, the idea of Openness can actually be productively pushed much further: for instance, the refereeing process itself is currently not following an open model, with decisions mostly taken behind closed editorial doors. As a consequence of this, refereeing remains completely uncredited despite representing a substantial investment in time and effort to the researchers who perform it. Some fields have already demonstrated the fact that the quality and usefulness of the refereeing process is greatly enhanced by more openness [7,8], but most scientific disciplines have not yet woken up to these benefits.

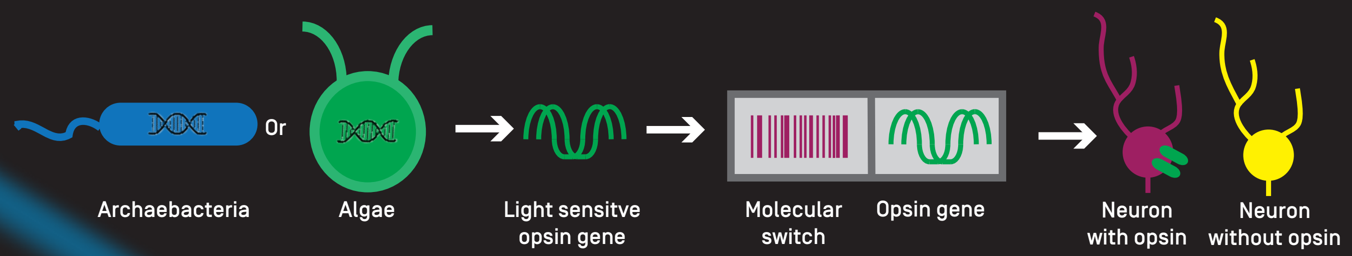
One can thus call for a much more profound transition than the one that is currently taking place: a transition to a truly Open implementation of the whole publication process, from submission through refereeing-improved publication all the way to post-publication feedback and impact evaluation (the latter representing yet another aspect for which a profound transition is needed).

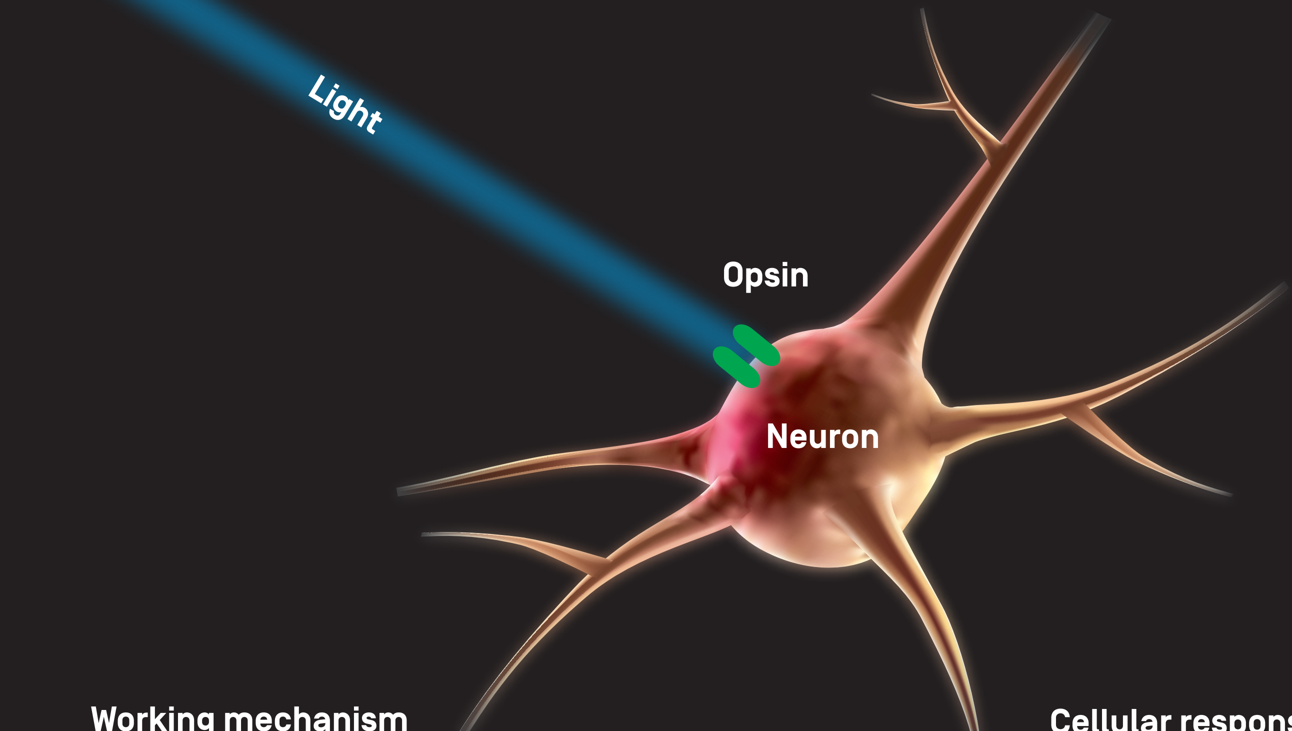
The inescapable fact that scientists are always best served by themselves led to the recent launch of SciPost, a non-profit foundation whose online portal SciPost.org offers a complete, truly open framework for publishing. But the transition will only take place if scientists make it happen by changing their own habits, this representing (perhaps somewhat surprisingly) the greatest obstacle. The comforting thought is that all elements are now in place for this transition to happen. The question is not whether science should be open or not. The real question which remains is: how open are you? Ω

→ References
1. http://english.eu2016.nl/documents/reports/2016/04/04/amsterdam-call-for-action-on-open-science
2. http://www.budapestopenaccessinitiative.org/read
3. http://legacy.earlham.edu/~peters/fos/bethesda.htm
4. https://openaccess.mpg.de/Berlin-Declaration
5. https://en.wikipedia.org/wiki/Open_access
6. http://www.scottaaronson.com/writings/journal.html
7. http://f1000.com
8. http://www.atmospheric-chemistry-and-physics.net/pr_acp_Poschl_FrontiersNeuroscience2012_MultiStageOpenPeerReview.pdf

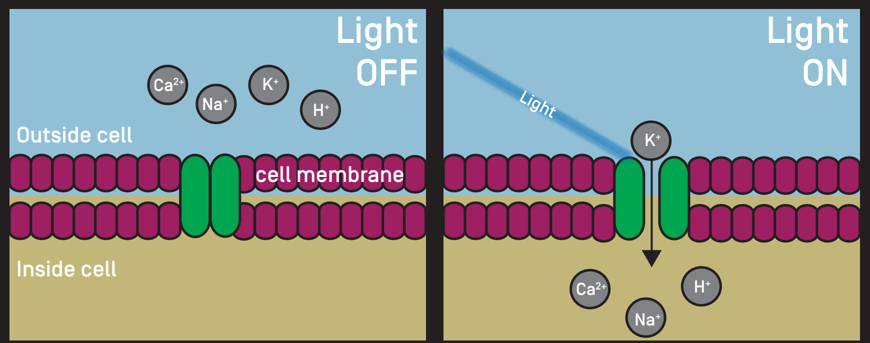
Optogenetics: lighting up the brain

Dubbed Method of the Year (2010, Nature) and Breakthrough of the Decade (2010, Science): optogenetics. While only developed eleven years ago, it is already an indispensable part of the neuroscientist's toolbox and used at all neuroscientific research institutes in Amsterdam. It exploits light-sensitive membrane proteins (opsins) derived from bacteria and algae, enabling researchers to manipulate neuronal activity on a millisecond timescale in a cell-specific manner, even in freely moving animals.



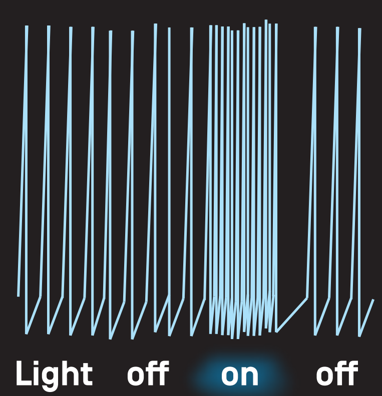


Working mechanism

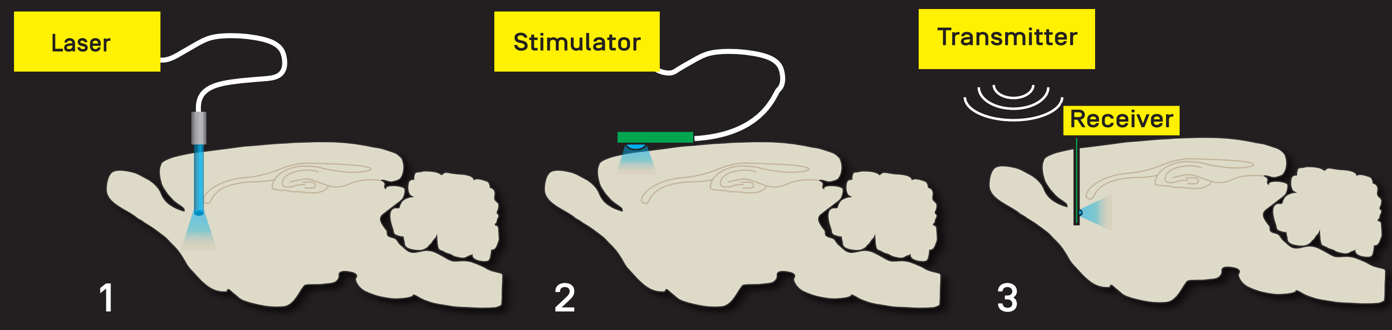


↑ **The 'activating' opsin Channelrhodopsin-2 (green) is inserted into the cell membrane (purple).** When blue light reaches the opsin, it opens and cations (Na^+, Ca^{2+}, H^+, and K^+) enter the cell, leading to cell activation. Use of different opsins (such as Archaerhodopsin or Halorhodopsin) can impart photoswitchable inhibition of the cell.

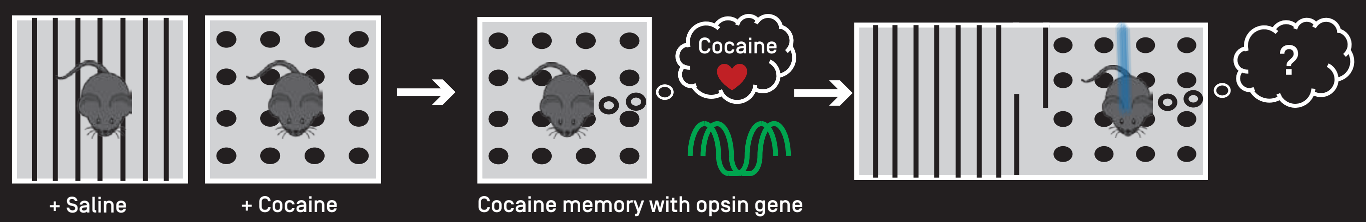
Cellular responses

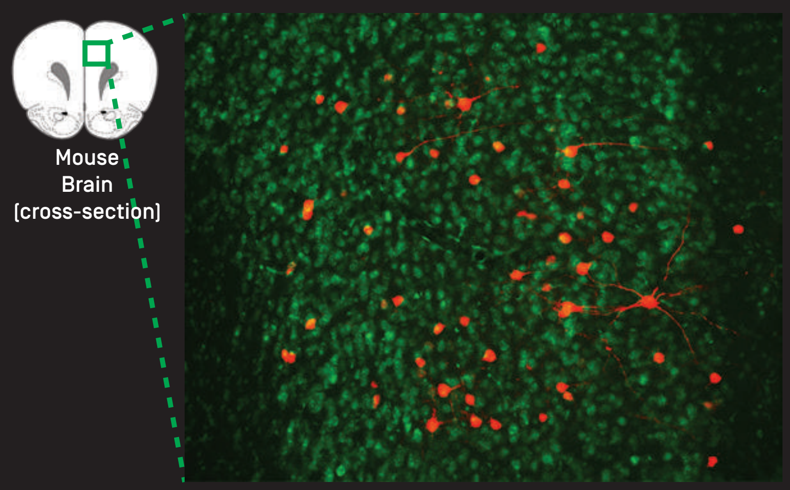


↑ **Electrical activity of a neuron expressing an 'activating' opsin.**



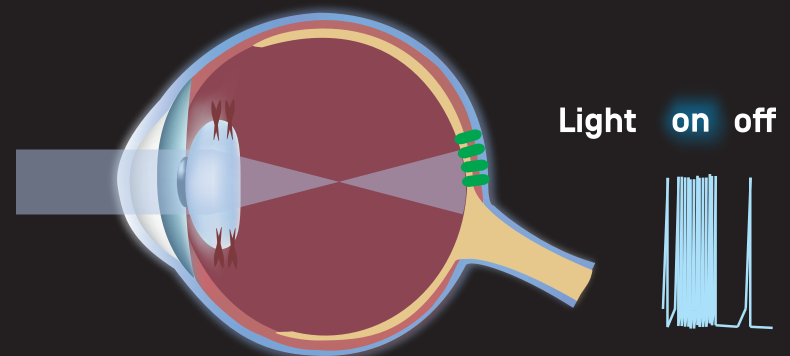
↑ **Light delivery methods (exemplified in a cross-section of a rat brain):**
1) Access to deep brain areas via a probe bringing in laser light through an optical fibre
2) Non-invasive access to superficial areas via external LED illumination on the surface of the brain
3) *In situ* light source in the brain wirelessly connected to transmitter allows free movement of the subject.





↖ **Application: highlighting a neuronal population associated with cocaine-memory in a mouse brain.**
Using optogenetics, researchers at the Vrije Universiteit manipulated neurons associated with drug memories. By exposing an animal to a context in which it previously received cocaine (top images), neurons that harbour the memory to cocaine could be labelled with an opsin. When these neurons were then activated using blue light, animals showed a decreased craving for cocaine. In this microscope picture you see the neurons associated with the cocaine memory in red and other neurons in green[1,2].

→ **Human application:**
A plan for a clinical trial has already been made in the United States. Here, opsins will be used to help patients with blindness caused by a disease where photoreceptors in the retina (yellow) are slowly lost. Vision can be restored by inserting opsins in the retina, using viral vectors, that react to blue light in the environment.



Optogenetics is expanding througout the life sciences, now all kinds of light switchable proteins are being developed. Its future shines bright!

1. Master's thesis Esther Visser, Research Master Brain & Cognitive Sciences, IIS-UvA. Research internship Memory Circuits - CNCR.Visser, E., Matos, M.R., van den Oever, M.C. (2015). The role of prefrontal cortex neuronal ensembles in expression of cocaine-associated memory. https://goo.gl/LwZ5BT
2. Image courtesy of M.R. Matos and Dr. M.C. van den Oever

By Huub Terra & Esther Visser
Center for Neurogenomics and Cognitive Research (CNCR), Vrije Universiteit, Amsterdam

Building synthetic cells to understand the biophysics of cell shape control

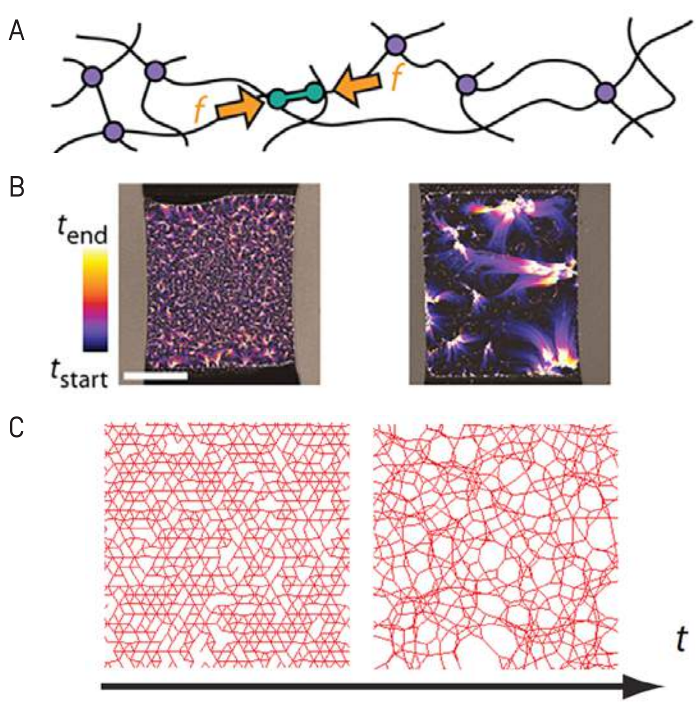
GIJSJE KOENDERINK heads the Biological Soft Matter Physics group at AMOLF and is affiliated professor at VU.

→ Cells are the smallest living building blocks of our body. Although we do not notice this in our everyday life, there is constant activity deep inside our body: cells are frantically changing shape as they grow, divide and crawl through tissues. This activity is essential to support vital functions such as tissue repair and immune responses. The question of how cells achieve cell shape control has developed into a research area where concepts and methods taken from physics are employed: biophysics. After all, cellular shape changes involve physical properties like cell stiffness and deformability. In our lab at AMOLF, we study the physics of cell shape control by rebuilding synthetic cells in the lab from the ground up. The basic idea is to combine a minimal set of cellular components into a cell-like system, and test if this system can mimic cellular functions. We were able to generate cell-like systems that exhibit muscle-like contractions and shape changes. The next challenge is to create more realistic synthetic cells to understand more complex functionalities such as cell division. This would allow us to contribute to puzzles in biology and health science. At the same time, cells provide us with fascinating design concepts for new materials that can morph and move as cells do.

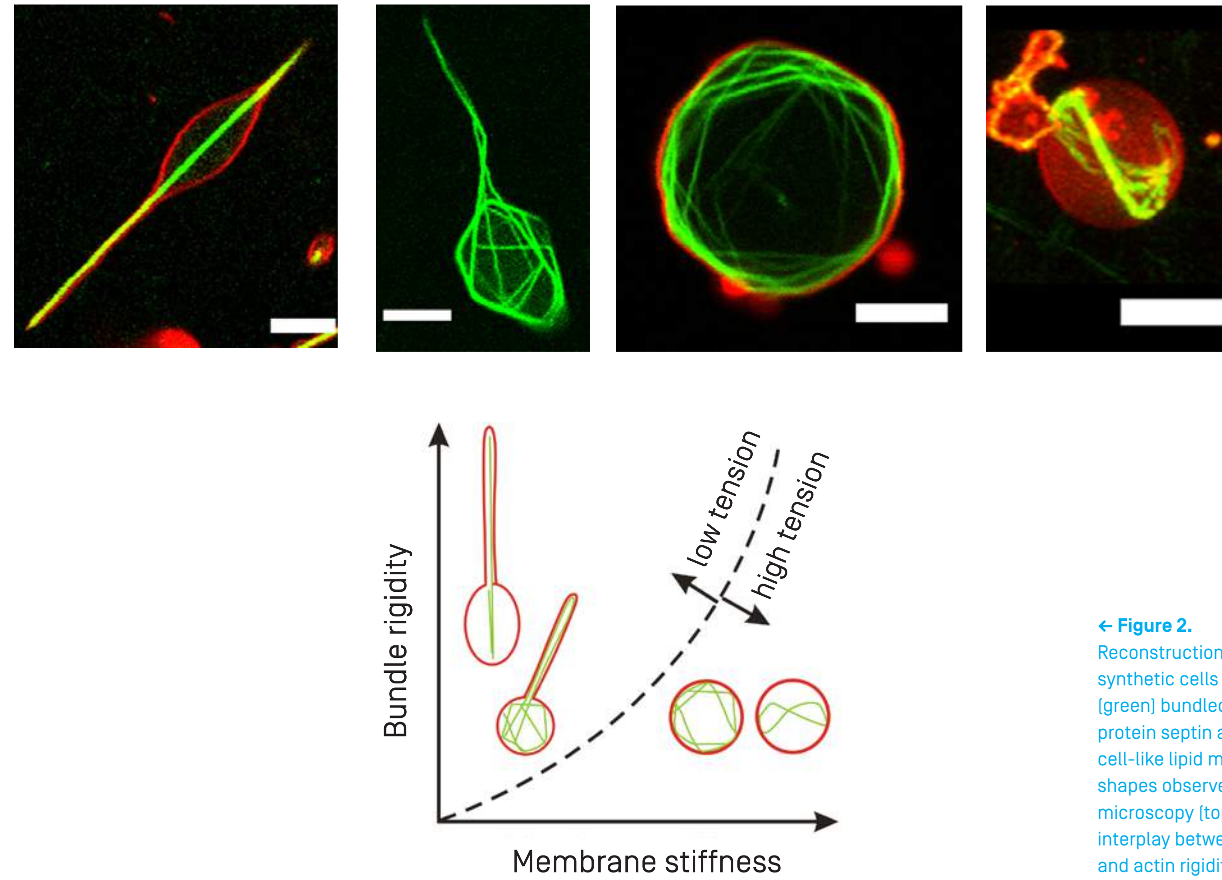
The cytoskeleton – muscle and bone of the cell
All cells in our body contain an active polymer called the cytoskeleton, which provides mechanical rigidity, but also allows cells to deform themselves. The term 'skeleton' is somewhat deceptive, because unlike the rigid bony skeleton that supports our body, the cytoskeleton that supports the cell is soft and dynamic. When viewed through a microscope, the filaments forming the cytoskeleton are constantly moving and waving. The reason for this difference lies in the difference in scale: bones are centimetre-sized and calcified, whereas cytoskeletal protein filaments have lengths in the micrometre range and diameters in the nanometre range. At this small scale, protein polymers are constantly in motion due to jostling by water molecules. Any micrometre-sized object, when placed in water, will perform a random walk known as Brownian motion. This is very useful for the cell, because it allows for spontaneous movement of proteins, nutrients and organelles driven by thermal motion. Thermal motion is most efficient in small systems, because diffusion is slow. In animal cells, thermal motion alone is not efficient enough to sustain cellular functions. Cells supplement thermal motion with active molecular processes that convert chemical energy supplied by nucleotides (ATP) into mechanical forces. The cytoskeletal filaments made of actin proteins use up ATP in order to actively grow and shrink at their ends, which generates pushing and pulling forces. Motor proteins such as myosin bind to the cytoskeletal filaments and use ATP to exert pulling forces on the cytoskeleton and to transport cargo vesicles along the cytoskeleton. The wild motions inside cells that we observe through a microscope are thus a combination of active molecular processes and spontaneous, thermally driven motion.

Rebuilding cellular contractions
All cells in our body change shape as they grow and divide. In addition, cells often have dedicated tasks that involve active shape changes. Our heart beats because muscle cells contract and relax. Immune cells that crawl through tissue detect and kill pathogenic bacteria. All these cellular shape changes are known to originate mainly in the actin cytoskeleton, through pulling forces generated by myosin motor proteins. However, it is not clear how these tiny (nanometre-sized) motors can cause an entire cell to contract, since each motor can only take nanometre steps and exert picoNewton forces. Cells somehow need to coordinate the activity of many motor molecules to act simultaneously across the entire cell. Studies of live cells identified a third essential component besides actin filaments and motor proteins: the so-called crosslinking molecules, which act as a molecular glue to hold the filaments together. We reasoned that the crosslinks are needed to transmit the tiny forces generated by the motors across the entire cytoskeleton. To test this hypothesis, we rebuild self-deforming active gels from a set of only three purified cellular proteins: myosin motors, actin polymers, and different cross-linker proteins, such as fascin or -actinin (see Figure 1).

By labelling each component with a fluorescent molecule, we can watch how active gels deform themselves under a fluorescence microscope. Consistent with our hypothesis, we found that the motors could only pull on the network and contract it when a threshold level of cross-linker proteins is present [1]. However, we observed that the gels ripped themselves into many small pieces when the crosslink concentration was well above this threshold. This was surprising, since existing physical models predicted that self-rupture should only occur right at the threshold. These models, collectively known as percolation models, predict that the threshold connectivity corresponds to the smallest number of connections between neighbours needed to keep a large group connected. This theory has been used to understand how electric power distributes across a grid, how water percolates through limestone or a bed of coffee grains, how fire spreads across a forest, or how computers connect across the internet. In all these cases, there is a sharp percolation transition. Surprisingly, the active gels have an unusually broad transition range that cannot be explained by any existing model. In order to understand why the percolation threshold kept reappearing, we collaborated with the theoretical physics group led by Prof. Fred MacKintosh (now at Rice University) from the VU University Amsterdam. They implemented a computer model of the active gels and discovered that the motors can actively pull off the crosslinks. This process allows gels that initially have many crosslinks, to lose connections until they reach a state resembling the percolation threshold. We confirmed this model in the lab by varying the concentration of active motors in the gel. We found that over-active gels exert such a force that they rupture themselves into shreds because too many crosslinks are detached. This work explains reported findings in the developmental biology literature, where depletion of crosslinks or upregulation of myosin activity have been shown to cause rupture of growing tissues during embryo development.



→ Figure 1.
Reconstruction of muscle-like cell contraction. **A**: the experimental model system: myosin motors (green) exert pulling forces (orange arrows) on actin filaments (black lines), which are connected via crosslink proteins (purple). **B**: Time evolution of contraction observed by fluorescence microscopy for a "sparsely" versus a "critically" connected network. Color codes for time in minutes, with [tstart, tend] = [2, 20] left and [2,120] right. Scale bar is 1 mm. **C**: Time evolution for an example network configuration.



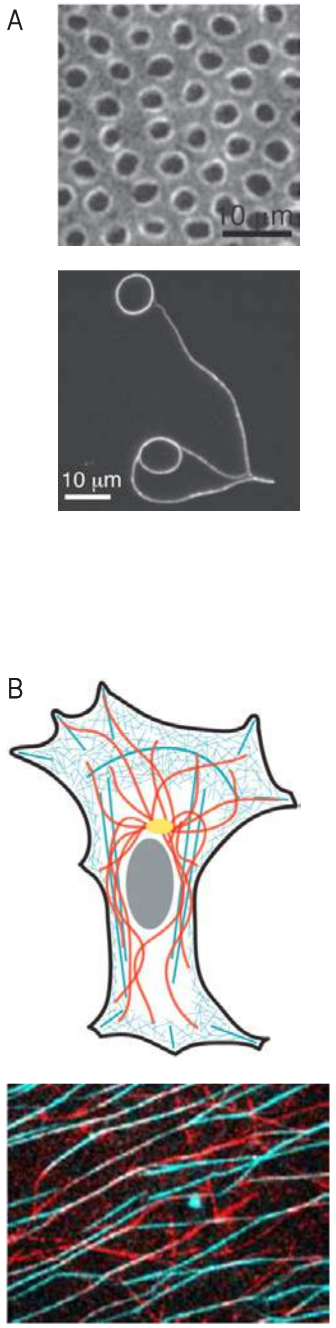
← Figure 2.
Reconstruction of cell shape control in synthetic cells where actin filaments (green) bundled by the crosslinker protein septin are encapsulated inside cell-like lipid membranes (red). The shapes observed by fluorescence microscopy (top) result from an interplay between membrane rigidity and actin rigidity (bottom).

"Cells often have dedicated tasks that involve active shape changes."

Rebuilding cell shape control
Shape changes of cells are not determined by the cytoskeleton alone, but also by the membrane that envelopes the cell to separate its contents from the environment. This membrane is made of phospholipids, which form a thin (~5 nm) and deformable layer all around the cell. The lipid membrane is weak and fragile, and therefore requires the cytoskeleton for elastic reinforcement. At the same time, the membrane requires the cytoskeleton to adopt different shapes, because by itself it would always be spherical. The reason is that lipid membranes have an elastic resistance against bending. Constricting the membrane during cell division or forming membrane protrusions during cell migration does not happen spontaneously, but requires active deformation by the cytoskeleton inside the cell. Meanwhile, the membrane also strongly affects the organisation of the cytoskeleton, because it confines the cytoskeleton to a small space. To understand cell shape control, we therefore need to combine cytoskeletal networks with lipid membranes to dissect the interplay of cytoskeletal and membrane mechanics.To create cell-like membrane encapsulation, we developed techniques that allow us to encapsulate controlled amounts of cytoskeletal proteins inside cell-like lipid membranes. The resulting cell-like systems are known as giant unilamellar vesicles (see Figure 2). We can control the stiffness of the vesicle membrane by changing the lipid composition (saturated/unsaturated fatty acids) or osmotically drawing out water from the ves- →

A

B



↑ **Figure 3.**
Towards more life-like synthetic cells. **A**: Reconstituted contractile rings that drive cell division in all eukaryotic organisms (top: images of contractile rings in developing fruit fly) by combining actin, myosin and the crosslinking protein septin (bottom). **B**: Cells polarize their shape and internal organization by coupling the actin (blue) and microtubule cytoskeletal (red) system (top). We can reconstitute actin-microtubule co-alignment by coupling the filaments with a crosslinker (bottom).

icle. We can independently control the stiffness of the encapsulated actin cytoskeleton by using crosslinking proteins that create rigid actin bundles. By systematically playing with these parameters, we discovered that the overall cell shape minimises the elastic energy of the whole system [2]. When the membrane is rigid and tense, it forces the actin filaments to bend and contort. In contrast, when the actin filaments form rigid bundles, they can force the floppier membrane to form long and narrow protrusions that resemble filopodia observed in neurons and white blood cells.

Bridging physics and biology
In the long run, it is our ambition to bridge the gap between the physical properties of cell-free model systems and living cells. To achieve this, we are developing ever more realistic cell-free model systems that incorporate more proteins known to be essential in cells. Together with the developmental biology groups of Dr. Manos Mavrakis at the Institut Fresnel in Marseille, we are working toward reconstituting cell division [3]. Cell division requires physical constriction of the cell membrane into two daughter cells. Constriction is powered by a contractile ring of circumferential actin filaments that is actively contracted by myosin motor proteins. Studies in developing fruit fly embryos showed that septin is an essential component of the contractile ring: when septin is depleted, cells can no longer form circular actin rings. By purifying septin and actin filaments and studying the system by both fluorescence microscopy and electron microscopy, we discovered that septins are able to bundle actin filaments into curved and tightly packed rings of actin filaments (see Figure 3A). This finding now provides a mechanistic basis of cell division defects observed in cells and developing embryos, such as mispositioning of the cytokinetic ring and multinucleation.

Together with the cell biology group of Prof. Anna Akhmanova at Utrecht University and the biophysics group of Prof. Marileen Dogterom at Delft University of Technology, we also try to go beyond the simple one-component cytoskeletal networks that we have studied thus far. Given its enormous molecular complexity, it is

"Research on the physical workings of cells can also pave the way for engineering smart materials."

common to study the cytoskeleton in terms of the three distinct functional subsystems: actin, microtubules, and intermediate filaments. However, cell biologists have found growing evidence that the cytoskeleton should actually be regarded as a highly intertwined entity (see Figure 3B). The three cytoskeletal subsystems are strongly coupled and instruct each other's organisation. This crosstalk is essential for cells to polarise: in the absence of cytoskeletal coupling, cells cannot migrate directionally nor properly position their contractile ring in the centre of the cell. We now work towards hybrid networks where we can study the mechanisms of linkage between cytoskeletal systems. We were able to reconstitute interactions between the microtubule and actin cytoskeleton using a microtubule-actin crosslinking factor, and discovered that this cross-linkers allows for accurate co-alignment of microtubules and actin [4]. This co-alignment is important for actively guide growing microtubules along stiff actin cables and organise directional cell migration. Conversely, growing microtubules can transport, stretch and even position actin filaments alongside microtubules, which can explain the formation of actin-based protrusions at the leading edge of motile cells. We are now extending these studies to include intermediate filaments, the most unexplored component of the cytoskeleton.

From synthetic cells to biology, but also to physics and materials
Building synthetic cells is a powerful route to understanding how a collection of lifeless molecules can together turn into a living cell. Synthetic cells also reveal the exciting physics that distinguish living from non-living matter: unlike non-living matter, living matter can deform itself and adapt to its environment by using up chemical energy to drive shape changes and process information. Our research is driven in equal parts by our fascination for the biology and the physics of cells. Research on the physical workings of cells can also pave the way for engineering smart materials. Active gels that mimic the mechanical properties of cells and tissues could help repair damaged tissue. Alternatively, synthetic active gels could allow soft robots to actively change shape and mechanically adapt to their surroundings. In the coming years we will explore these opportunities together with several groups that newly joined AMOLF (van Hecke, Noorduin, Overvelde) to develop a field called 'Designer Matter'. Ω

→ **References**
1. J. Alvarado, M. Sheinman, A. Sharma, F.C. MacKintosh, G.H. Koenderink. *Nature Physics* 9, 591-597 (2013)
2. F.C. Tsai, G.H. Koenderink. *Soft Matter* 11, 8834-8847 (2015)
3. M. Mavrakis, Y. Azou-Gros, F.-C. Tsai, J. Alvarado, A. Bertin, F. Iv, A. Kress, S. Brasselet, G.H. Koenderink, T. Lecuit. *Nature Cell Biology* 16, 322-34 (2014)
4. M. Preciado Lopez, F. Huber, I. Grigoriev, M.O. Steinmetz, A. Akhmanova, G.H. Koenderink, M. Dogterom. *Nat. Comm.* 5, 4778 (2014)

MICHIEL BUCHEL, general director and chairman of the board of NEMO in Amsterdam, the largest science centre of the Netherlands.

1. The first experiment I ever did was...
... probably trying to drink milk with my eyes open ... but the one I clearly remember is playing with my Electricity Science Kit. My father was watching football and I wanted to scare him with the little electric bell that was in the box. I hid behind my father's chair and plugged it into the 220-Volt wall socket. The next moment there was a big spark and all the lights (and the TV) turned dark. Then I felt my father's hand. So I learned that playing with electricity is not without danger.

2. My constant source of inspiration is...
... our planet Earth and our relationship with it.

3. One book that I recommend to all young scientist is...
... *A Short History of Nearly Everything* by Bill Bryson. This book is a tribute to science and to curiosity. Scientists are driven by curiosity: how do things work? The book describes this in a fun and easily understandable way.

4. If I headed the first Ministry of Science the first thing I would change is...
... the support for science centres and museums in the Netherlands. Increase it! I would love to have a Dutch Museum for Science and Technology for both children and adults. These centres can help to further develop our society and to create a societal debate.

5. If I had to switch roles with a famous person for 1 day, I would choose to be...
.. King Willem-Alexander, but as the 'Willy' character as created on TV by Sander van de Pavert.

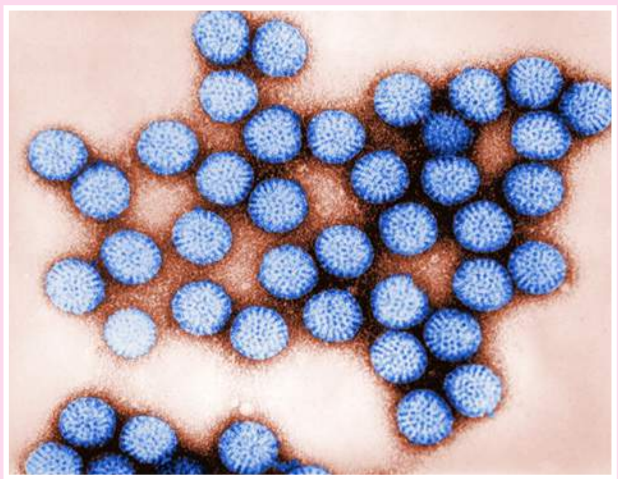
6. I am most creative when...
... I'm doing nothing. I think it is incredibly important if you work in an office in front of a screen for the bigger part of the day, you take time to empty your head. Just staring at the sky helps me; I do this every day for 15-30 minutes. I'm 60 years old now, and I think this method has helped me to come up with new ideas and to prevent me from suffering a burnout. I can surely recommend it.

7. If I could choose my field of study once again I would choose...
... history. I think everyone is convinced he or she lives in a unique period of history, but by gaining more knowledge and a better understanding of the past you can understand present and future developments even better.

8. I would like to share the following with the Science Community in Amsterdam...
We, as Dutch, should be more proud about the great scientists and engineers we had and still have. They brought us such improvement of the quality of our lives and we should be aware of this. Japanese students visit the birthplace of the great Christiaan Huygens, but many Dutch people don't even know who he was. Scientists can play an important (and authentic) role to improve this, by sharing their passion and the relevance of their work with a large audience. I also think this can be very effective to stimulate more students to choose for beta-oriented education.

Gut bacteria: new modulators of rotavirus vaccines?

BAS HAAK MSC is now PhD student at the Academic Medical Center (AMC).



↗ **Figure**
Transmission electron micrograph of rotavirus particles. *(source: Center of Disease Control and Prevention (CDC), Atlanta, Georgia, USA)*

→ **A rotavirus infection is the leading cause of severe diarrhoea and kills more than 200,000 children each year, primarily in Sub-Saharan Africa and Southeast Asia. An additional problem is that, in these developing countries, oral vaccinations against rotaviruses show a significantly reduced efficacy compared to that in developed countries.**

Numerous hypotheses exist about the cause of the reduced efficacy of rotavirus vaccines in developing countries, but none can fully account for this dramatic difference. Recent clinical studies in Ghana and Pakistan suggest that differences in the intestinal microbiota - the bacteria in infants' intestines - may help explain why oral vaccines are less effective in poorer settings. The intestinal microbiota can be regarded as a complex ecosystem consisting of trillions of bacteria, of which the largest and most heterogeneous communities are found in the gastrointestinal tract. Disruption of homeostatic microbiota has been associated with an increased susceptibility to numerous intestinal infections. In order to understand potential underlying causal mechanisms of reduced efficacy of rotavirus vaccines in developing countries, it is important to study microbiota-rotavirus interactions in greater detail, including by manipulating them. My Master's thesis project therefore aimed to describe a mouse model that measures whether specific micro-organisms in our gut are involved in the immune response against rotavirus. We designed two preclinical mouse models involving young adult and neonatal mice. From each age group, we fed groups of genetically identical mice with different combinations of antibiotics to attack the intestinal microbiota. Subsequently, all mice were exposed to a mouse variant of the rotavirus, and we measured to what extent the immune system of the mouse was affected. As a read-out for severity of rotavirus infection, we measured the amount of viral particles in the faeces, and performed visual diarrhoeal scoring.

"Differences in the intestinal microbiota may help explain why oral vaccines are less effective in poorer settings."

The serum of mice was isolated pre- and post-infection to assess the levels and the activity of several immune cells.

It appeared that, when treated with a combination of broad-spectrum antibiotics (such as ampicillin, vancomycin, neomycin and metronidazole) prior to rotavirus infection, young adult mice had both significantly increased amounts of rotavirus particles and higher levels of active immune cells post-infection when compared to treatment with no antibiotics or just one type of antibiotic. In neonatal mice, immune responses were significantly higher compared to the young-adult counterparts. Yet, neonatal mice did not differ in their immune responses when pre-treated with any of the broad-spectrum antibiotics. Despite this lack of immune response, pre-treatment with vancomycin decreased the amount of rotavirus particles. On the other hand, pre-treatment with neomycin or metronidazole led to both a significantly higher disease severity and viral replication.These results suggest that changing the population of intestinal bacteria can impact rotavirus clearance in both young-adult and neonatal mice. Although we don't know yet how the microbiota composition was influenced by antibiotics, we hypothesise that the presence of a specific type of bacteria impairs rotavirus replication, which results in enhanced protection against the infection. The specific mechanisms that drive these protective responses remain to be further elucidated. In order to further understand the pathophysiology of microbiota-rotavirus interactions, I recently started a PhD project at the AMC, in which I will try to fine-tune these models and work on a human-volunteer trial. Our team hopes that future breakthroughs in the understanding of the immunological responses towards rotaviruses and efficacy of rotavirus vaccines could help to better protect vulnerable children worldwide from diarrhoeal diseases. Ω

→ **Reference**
B.W. Haak, The influence of the gut microbiota on rotavirus immune responses. Master's thesis, University of Amsterdam (2015).

Topological insulators

EMMANOUIL FRANTZESKAKIS worked as a postdoctoral researcher at the Institute of Physics, UvA and recently moved to a faculty position at the Université de Paris-Sud.

→ **Everyone knows that insulators are materials that do not conduct electricity. New kids on the block are called Topological Insulators (TIs for short). In a pure crystal of a three-dimensional TI, the *inside* of the crystal – the bulk - does not conduct electricity. However, the edges of the crystal - the *surfaces* - do. They don't just happen to be metallic, theory tells us they are forced to be metallic by fundamental mathematical symmetries of nature.**

For the electrons in a regular computer chip, the energy of the electrons (E) is linked to the square of their momentum (k^2), known as the dispersion relation. The signature of these newest members of the weird but wonderful quantum family is that the dispersion relation of the conducting electrons at the surface is linear: , giving what is known as a Dirac cone in 2D. When measured using the photoelectric effect, Dirac electrons show a characteristic V-for-victory dispersion trace, sketched in orange in the top part of the figure.

Enter real life, stage left....
Recently, researchers at UvA's Institute of Physics were doing such photoelectric measurements using a sort of super-microscope called a synchrotron. They noticed the special V-for-victory dispersion relation (orange in the figure) quickly gets contaminated with regular, parabolic states from the bulk of the crystal (blue in the figure), due to something called band-bending. Thus the cool Dirac states are drowned out by Schrödinger's minions, and this would appear to scupper the chances of using the former in future quantum information technologies.

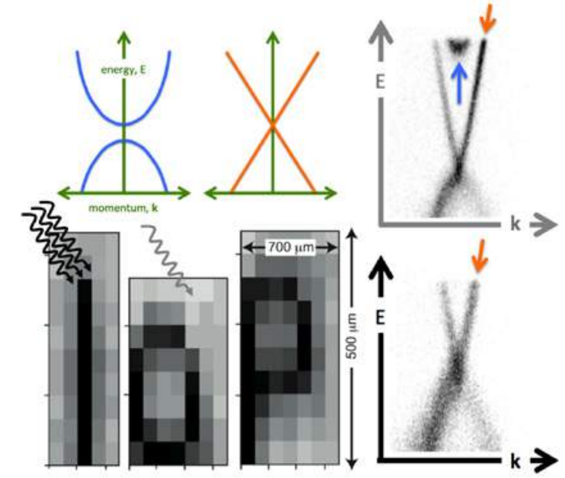
Bright idea
The bands bend because of a local electric field, a little like how electrons move when a voltage is applied to a copper wire. The light from the synchrotron excites electrons from occupied states into what used to be unoccupied states. The *holes* ('missing electrons') thereby created in the formerly occupied states are positively charged and newly occupied states themselves negatively. We realised that if we make these two charge clouds populous enough, when they move in opposing directions in the electric field (similarly to how a photovoltaic solar cell works) they will exactly compensate the band bending, and flatten the bands again. This would erase the Schrödinger states, leaving the special Dirac states as victors with the V-like dispersion to prove it. As we have designed the TI crystal to have a minimal bulk conductivity, these charge clouds would stay put laterally, allowing us to dial-in a local change in the energy landscape on the scale of the few-micron-wide synchrotron light beam. Thus, we set out to write lines in the topological electronic landscape using our (admittedly pricey) light source turned up as bright as it would go, and then we used the photoelectric effect with a gentler beam to examine the result.

"Erasing show-stopping bulk electronic states."

It worked. The team, in an apparent homage to their employer, used this new technique of photovoltaic writing to spell out the first three letters ever to be written in topological Dirac states: I o P. The lighter pixels are where the intense photon beam had not been put to work, and their photoelectric effect image reveals how the show-stopper Schrödinger states from the bulk (blue) show up as a shallow parabola in the centre of the Dirac-'V' shape (orange). The dark pixels that were 'written', are regions with purely linear dispersion relations (Dirac only!), as demonstrated in the lower photoelectric effect image.

Laser pointer or LED
Not everyone has access to a synchrotron, yet our experiments show that the flux density - number of photons per mm² per second - of a simple laser pointer or commercial LED is also sufficient to have the same effect. This research shows how we can reinstate the primacy of the all-important Dirac electrons at the surface of topological insulators by blocking the Schrödinger electrons, paving the way towards using the special properties of the Dirac electrons in future devices. Ω

→ **Reference**
E. Frantzeskakis, N. De Jong, B. Zwartsenberg, Y. K. Huang, T. V. Bay, P. Pronk, E. Van Heumen, D. Wu, Y. Pan, M. Radovic, N. C. Plumb, N. Xu, M. Shi, A. De Visser, and M. S. Golden, Micro-metric electronic patterning of a topological band structure using a photon beam, *Nature Scientific Reports* 5, 16309 (2015).



→ **Figure**
Parabolic Schrödinger electrons (blue) and the linear dispersion of topological, Dirac electrons (orange). A UV beam is successfully used to pattern narrow lines in the energy landscape of a topological insulator: dark pixels possess only Dirac electrons, as demonstrated in the photoelectric effect image shown right of the "IoP".

Poison pills and antidotes: protecting relevance feedback in data searches

MOSTAFA DEHGHANI is PhD student at the Institute for Logic, Language and Computation (ILLC), UvA.

→ Reference
M. Dehghani, Significant Words Representations of Entities, In Proceedings the 39th International ACM SIGIR Conference on Research and Development in Information Retrieval (2016)

→ Nowadays, no matter how complicated the information needs of users are, search engines satisfy them by providing useful and relevant results. They do not merely rely on a few keywords that users submit as queries, but additionally analyse their previous click behaviour. In this regard, one of the techniques search engines employ is called 'Relevance Feedback' (RF). In a typical RF scenario, the user submits a query to the search engine (SE). The latter returns a ranking list of web pages based on the user query and the user then clicks on some of the retrieved results. The SE assumes the clicked pages hold relevant information, and adds keywords from their content to the user query. When the user continues searching, the SE is therefore able to provide better results. However, some of the pages clicked on by the users may contain irrelevant words, which mislead the RF mechanism. These pages are called 'Poison Pills' in the trade. To tackle this problem, we proposed a method in which a model is estimated from the content of the clicked pages that exclusively captures the words that represent significant commonalities. Put loosely, our approach iteratively removes two types of words from the model: *general words*, i.e., common words used frequently across all the web pages on the web, and *page-specific* words, i.e., words mentioned in some of the clicked pages, but not the majority of them (see Figure). Indeed, when put to the test, this approach prevents noise words interfering with the relevance feedback, and thus successfully improves your search results by protecting RF against Poison Pills. Ω

↓ figure caption
Improving search results by relevance feedback. Significant words for query expansion are expected not to occur frequently in all the web pages (general words), but should also not occur in only one of the clicked pages (specific words).

A non-academic career after your PhD?

LAURA JANSSEN, advisor Science Communication, Faculty of Science, VU .

← Figure
Participants during the course 'Employability Outside Academia' run by the PCDI in February 2016
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For more information:
www.pcdi.nl
www.rathenau.nl
www.uva.nl/fnwi

→ Only 30 percent of the postdoctoral researchers are able to find a job in science, according to the latest numbers of the Rathenau Institute on this subject (survey of April 2013). So this means that 70 percent leaves the university, voluntarily or not. Meanwhile, there is an ever growing number of PhD students. The Rathenau Institute states (in the same survey) that the number of PhD defences in the Netherlands has doubled since 1990: from about 1,900 to more than 3,700.

Develop broad skills
The Postdoc Career Development Initiative (PCDI) is a commercial organisation that "aims to stimulate the broad professional and career development of researchers who (are about to) have a PhD, in order to get the most out of their potential", the PCDI says on her website. "PhD students mostly focus on achieving scientific excellence and scientific skills. In this they are supervised and stimulated. Of equal importance, however, is that they develop other skills, not only for their scientific career, but also for a career outside academia". The PCDI was originally funded by the Dutch Ministry of Economic Affairs. The initiative was established in 2007, initially focusing on facilitating young scientists to make the transition to areas outside academia. Nowadays, the PCDI creates awareness, offers courses, brings together companies and researchers, and influences politics and policy makers.

Ambassadors
Several knowledge institutes in Amsterdam work together with the PCDI and use its expertise, such as VU, UvA, AMC, VUmc and the Netherlands Cancer Institute (NKI). At these institutes, PCDI is supported by local 'ambassadors'. Mostly, these are PhD students or postdocs that are actively working on their career development and would like to propagate the importance of this within their network. A popular course to begin with is the course 'Employability Outside Academia'. The course (in English) consists of three one-day sessions in a 3-month period. Questions discussed are: What is the added value of my PhD? What are non-academic employers looking for? How can I find out what career suits my profile and interests best? Ω

Alumni @Work

Where do the alumni of the science institutes and faculties in Amsterdam end up in the worldwide job market? This item zooms in on two alumni who chose a different path after having finished their doctorate degree.

Bruno Dagnino

Co-founder of start-up Metrica Sports and former PhD student in cognitive neuroscience at the Netherlands Institute for Neuroscience (NIN).

"During the 3rd year of my PhD I already decided I didn't want to stay in academia and that I wanted to do something in the private sector. Originally I thought about using my data analysis skills at a football club. I shared this idea with two friends who also expressed their desire to do something similar. We played with the idea for a while and about a year before the end of my contract as PhD candidate we decided to take it seriously and started working on a business plan in our spare time (nights and weekends).

One of the things we did was to validate if there was an interest from the market. Apparently there was, and soon we built the first prototype of our product. That was the beginning of Metrica, our own company. The concept of Metrica is that it helps football teams improve their performance through video and data analysis solutions.

The day I left the NIN, I started working full time in our start-up. My days are spent for 50% of the time on 'managerial' tasks such as meetings and decision making, and the other 50% on coding. I didn't really know how to do any of those things, other than a bit of programming. I am – as they say – learning on the job every day.

What I like most about my current job is that it is very dynamic. The problems and challenges are changing all the time. The downside of this is the uncertainty: you don't really know how you are supposed to do what you have to do. But the upside is that you are constantly learning. Compared to academia I experience it as a much more dynamic environment, and you get to see the results of your work really fast. That's one of the things I like best. Ω

Insider's advice
I knew I could do valuable science, but I thought building a valuable product, or something people would pay for, was out of my league. I was wrong. The most fundamental advice I can give to anyone who wants to transition from academia to entrepreneurship is: don't doubt yourself.

Nikhil Pandya

Postdoctoral fellow at Hoffmann-la Roche and former PhD candidate at the Centre for Neurogenomics and Cognitive Research, VU.

Since the time I did my first research project in a lab in early 2007, I knew I wanted to pursue research as a career. My work back then was in synthetic organic chemistry and as is the case with most people, the first stint in the lab opened my eyes to many things about research: both positive and negative. Clearly, for me, the excitement of research by far outweighed the downsides such as long working hours.

Fast forward 3 years and I found myself happily pipetting around in the Neuroproteomics lab at the Centre for Neurogenomics and Cognitive Research of VU Amsterdam. My PhD was primarily focused on answering basic questions about Glutamate receptor proteins in the brain. Although interesting, I found it difficult to extrapolate our findings to benefits that would have implications in understanding disease. Often, I would be recited cases of neuropsychiatric disorders and be asked to give an opinion about it by family and friends. This, along with the fact that a lot of funding was primarily directed towards research on neuropsychiatric disorders, made it clear to me that the next step would have to be in more applied research.

Then came the dreaded time in every PhD candidate's life; I had to think of next steps. After a quick survey of the available positions in pharma companies, it was clear that there were multiple ways, but not all suitable for scientists with a doctorate degree. Positions such as senior scientist or junior scientist demand an extensive publication record and experience as a postdoc. Of all the options, industrial postdoc seemed the most applicable. In theory I could still perform basic research, while being exposed to applied research all around me.

It has been a couple of months that I joined Roche's Pharma Research and Early Development site in Basel, Switzerland. So far, the journey has been absolutely fantastic. People are extremely helpful and each project involves experts from different technology platforms and biologists working in perfect synchrony. I find myself lucky to be associated with a drug development programme and get exposed to early clinical development, along with ideas and tools on how to proceed with my basic research questions. And in terms of resources, the labs are extremely well equipped and funded. Ω

Insider's advice
All in all, I would highly recommend students in academia to consider postdocs at big (pharma) companies. With respect to smaller companies, project objectives should be clear, in particular if one is interested in pursuing a research career.

Puzzle

Which gift did Lisa buy for Susan?

Frank, Sarah and Lisa are friends with Susan. Susan is graduating, so the other three wanted to get her some graduation gifts. They went out together on Saturday and all liked a number of items to pick from. For each item, they also liked several options at different pricaes, of which Sarah carefully took notes to help them later when buying their gifts.

Sarah's notes included the following:

Gloves	15	18		*euros*
Hat	16	28		*euros*
Scarf	12	18	24	*euros*
Book	15	12	16	*euros*

On Sunday, Lisa went back to the stores and of the above items she bought Susan the one that she liked best. She then told Frank only the name and Sarah only the price of her graduation gift for Susan, and asked both of them to guess which specific one of the above options she had picked, without telling each other the exact name or price.

Frank: I don't know which specific choice Lisa has made for her graduation gift for Susan, but I am certain that Sarah does not know either.

Sarah: At first, I didn't know what specific choice Lisa has made for her graduation gift, but now I know.

Frank: Then I also know which choice Lisa has made.

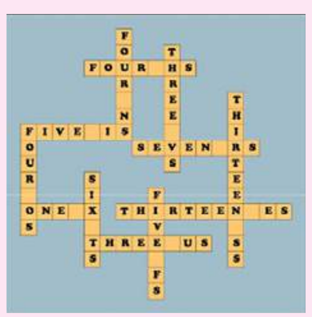
win
the first ten correct answers will win an Amsterdam Science T-shirt

Mail the answer to
amsterdamscience@gmail.com

before
1 January 2017

The answer to the puzzle in issue 3

The solution to the puzzle in issue #3 of Amsterdam Science magazine was:



@ Lee Shallows and Victor Eijkhout

Congratulations to the winners below, who sent the correct answers and won an Amsterdam Science t-shirt:

Joachim Goedhart
Taddeüs Kroes
George Jenkinson
Isaías Roldán
Diewertje Bink
Jasper Jasper
Birte Zuidinga
Matthijs de Geus
Ricardo Paap
Vincent Blum
Arnoud Visser

Open Access: spreading the seeds of science

If you like to design a puzzle yourself, please send it to amsterdamscience@gmail.com, and we'll consider it for the next issue of Amsterdam Science magazine.

Short information about the magazine

www.amsterdamscience.org

→ **Amsterdam Science** gives Master's students, PhD and postdoc researchers as well as staff a platform for communicating their latest and most interesting findings to a broad audience. This is an opportunity to show each other and the rest of the world the enormous creativity, quality, diversity and enthusiasm that characterises the Amsterdam science community. Amsterdam Science covers all research areas being pursued in Amsterdam: mathematics, chemistry, astronomy, physics, biological and biomedical sciences, health and neuroscience, ecology, earth and environmental sciences, forensic science, computer science, logic and cognitive sciences.

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One of the editors will contact you, primed to hear about your exciting story or striking image, and to discuss with you how it could reach a broad audience via publication in the magazine.

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New Realism

New scientific ideas challenge us to transcend our limits, as modern science explores the length and time scales that lie beyond the world we see and beyond our everyday imagination. This spring, the exhibition 'New Realism: The Gaze of Science' took place at the Amsterdam Science Park, supported by Nikhef, AMOLF, UvA's FNWI and the Amsterdam Fund for the Arts. Collaborations between artists and scientists were central to the exhibition, which featured imagery featured from more than fifty scientists from Amsterdam.
Coming up: New Realism will launch an 'Artist in Residence' programme, so as to cement the ties between art and science in Amsterdam. See www.newrealism.org for more information.Ω